Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Brain Tumors

Eric T. Wong, M.D.

Brain Tumor Center & Neuro-Oncology Unit

Beth Israel Deaconess Medical Center

Dana Farber/Harvard Cancer Center

Harvard Medical School

Boston, Massachusetts

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Disclosures

Research Grants:

A Reason To Ride Research Fund

AstraZeneca

Five Prime Therapeutics

Immunocellular Therapeutics

Merck

Northwest Biotherapeutics

Novocure

Pfizer

Plexxicon

Vascular Biogenics

ZaiLab

Primary & Metastatic Brain Tumors

TABLE 1. HISTOLOGIC CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM.*

- **Tumors of neuroepithelial tissue**
- Astrocytic tumors
  - Astrocytoma
  - Anaplastic astrocytoma
  - Glioblastoma multiforme
  - Pilocytic astrocytoma
  - Pleomorphic xanthoastrocytoma
  - Subependymal giant-cell astrocytoma
- Oligodendroglial tumors
  - Oligodendroglioma
  - Anaplastic oligodendroglioma
- Mixed gliomas
- Pineocytoma
- Pineoblastoma
- Embryonal tumors
  - Medulloblastoma
  - Primitive neuroectodermal tumor

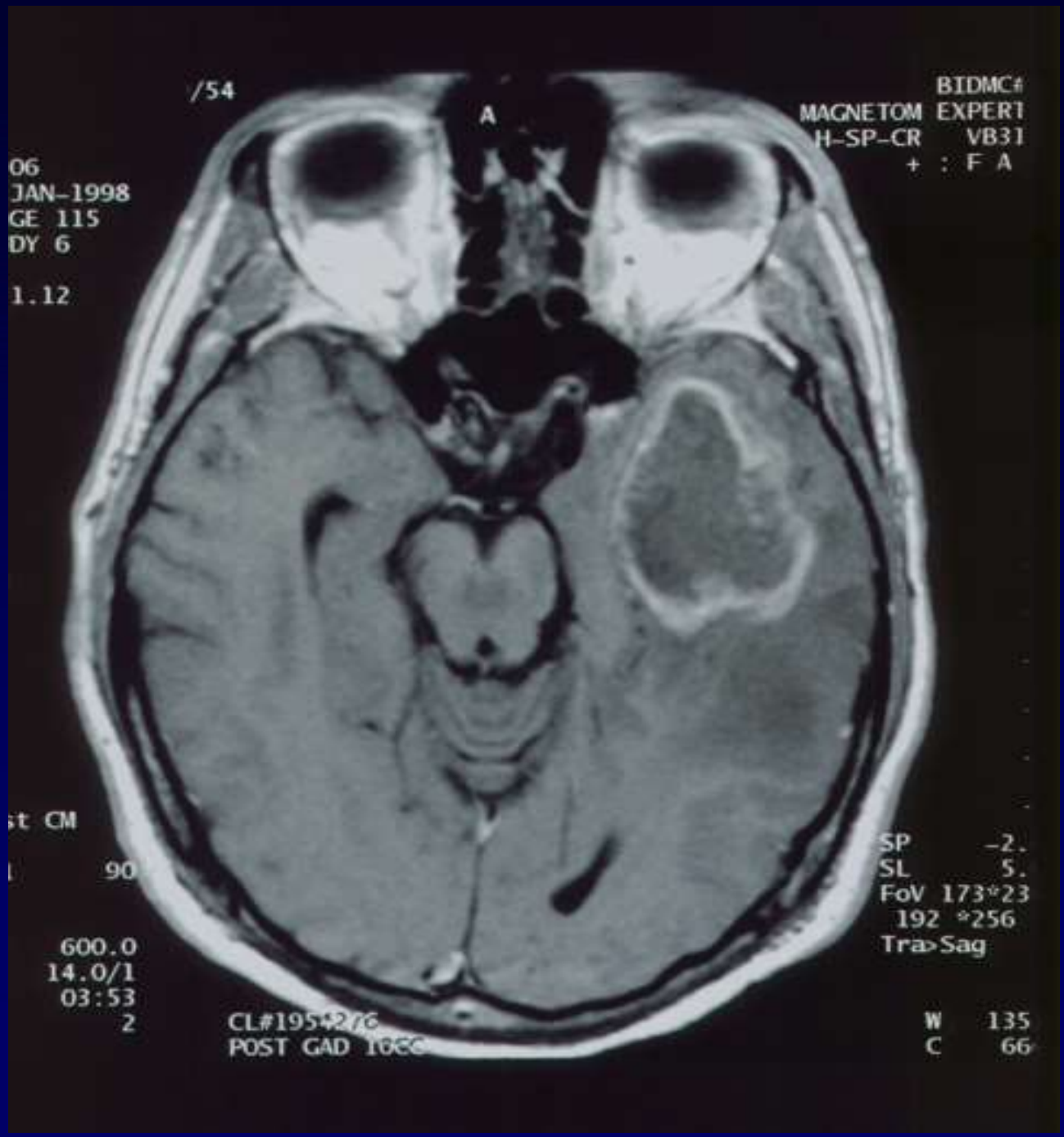
Table 3. Tumor Types, Metastatic Neurological Complications, and Percentage of Inpatients with Each Tumor Referred to Neurology Service

Primary Site	Pain Due To Bone Metastasis Only	Brain Metastasis	Epidural Extension or Metastasis	Tumor Plexopathy	Meningeal Metastasis	Paravertebral Radiculopathy	Base-of-Skull Metastasis	Total (Inpatient)	Admissions to MSKCC	Percentage of Inpatients Referred
Lung	18	64	11	3	10	4	2	153 (129)	821	15.7
Gynecological[b]	3	6	1	5	...	1	...	30 (20)	184	10.9
Other gastrointestinal[c]	1	...	2	...	...	...	...	29 (21)	325	6.5
						2	...	28 (27)	257	10.5
						...	2	18 (11)	129	8.5
						1	...	15 (13)	72	18.1
						...	...	9 (8)	55	14.5
						1	...	91 (73)	637	11.5
						23	22	855 (670)	5,147	

Primary Site	Pain Due To Bone Metastasis Only	Brain Metastasis	Epidural Extension or Metastasis	Tumor Plexopathy	Meningeal Metastasis	Paravertebral Radiculopathy	Base-of-Skull Metastasis
Lung	18	64	11	3	10	4	2

Astrocytic tumors
Astrocytoma
Anaplastic astrocytoma
Glioblastoma multiforme

DeAngelis LM. *N Engl J Med* 2001;344:114-123; Clouston PD, et al. *Ann Neurol* 1992;31:268-273.


/54
A
BIDMC#
MAGNETOM EXPERT
H-SP-CR VB31
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06
JAN-1998
GE 115
DY 6
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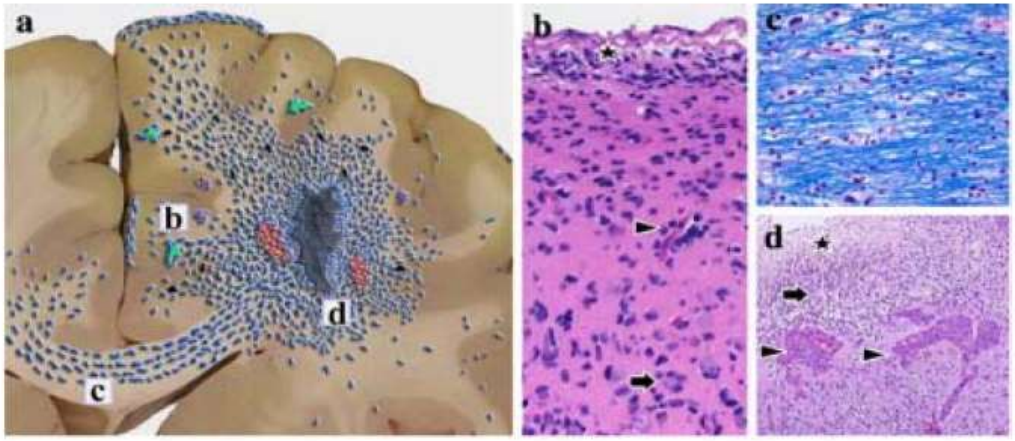
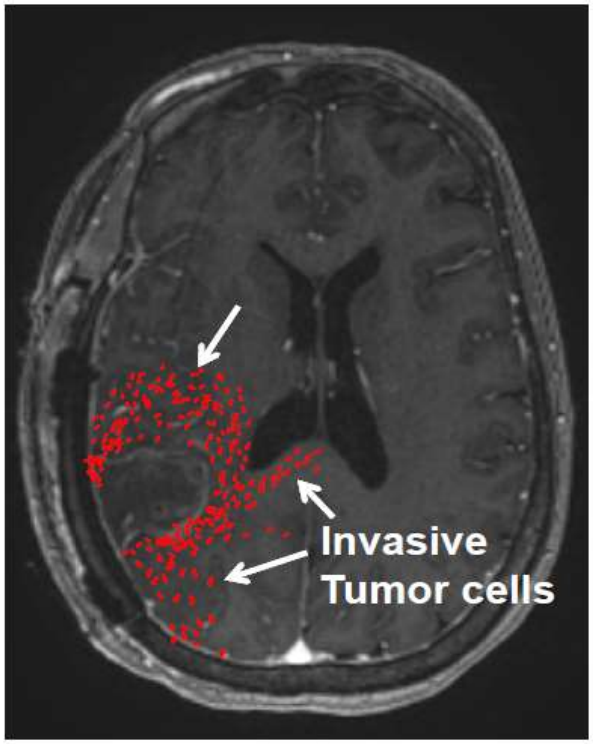
st CM
90
600.0
14.0/1
03:53
2
CL#195+276
POST GAD 10cc
SP -2.
SL 5.
FoV 173*23
192 *256
Tra>Sag
W 135
C 66

Impossible to Resect All Glioma Tumor Cells

- Invasive and infiltrative tumors
- Difficult to visualize tumor and perform maximal EOR
- Residual tumors cells outside of contrast enhancing margin
- Almost all recurrences local

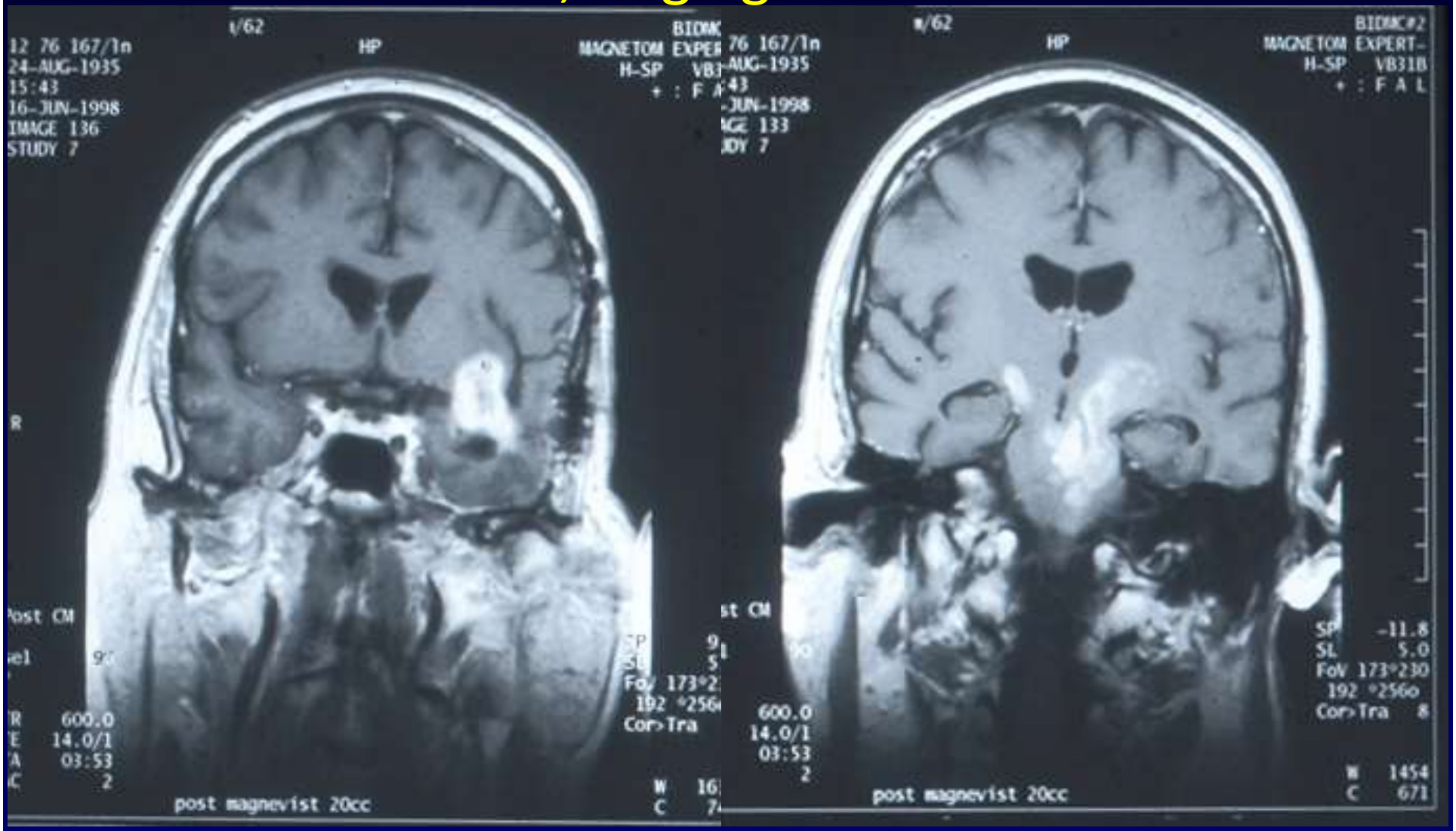




Postop MRI T1 w/Gad

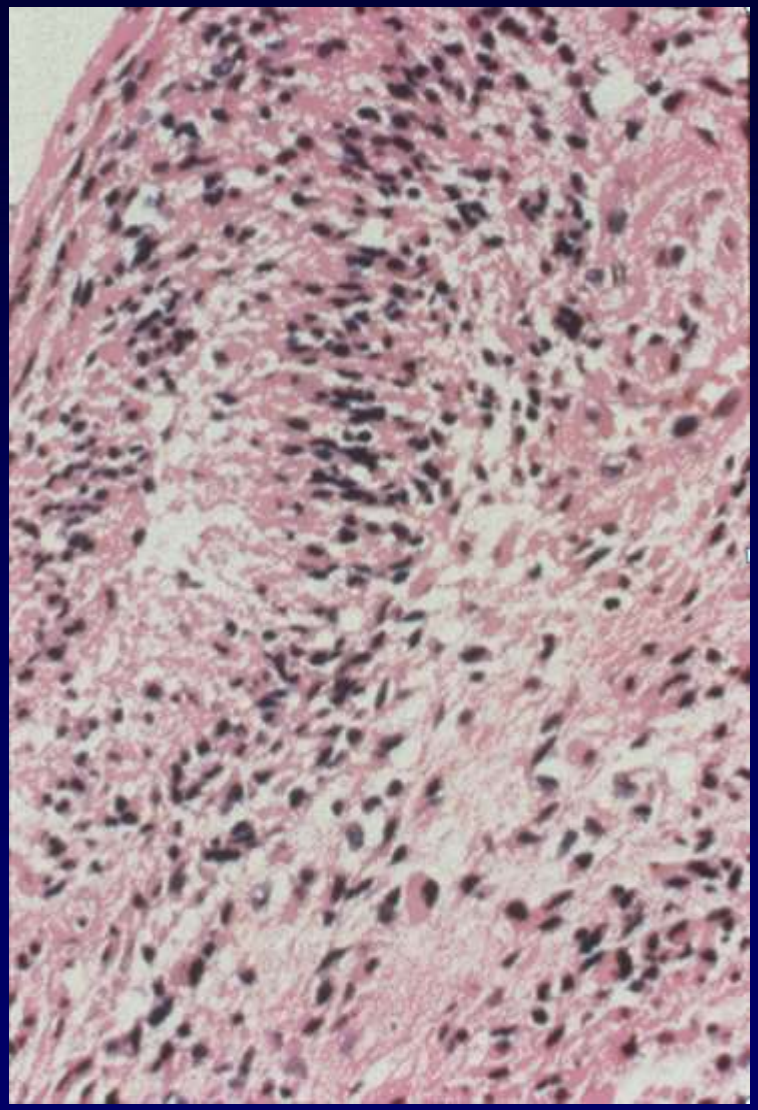
Claes A et al. *Acta Neuropathol* 2007; Kelly PJ et al. *J Neurosurg* 1987.

Hallmarks of Glioblastoma: Tumor Growth, Angiogenesis and Invasion



Wong ET. *J Neurooncol* 2006;77:295-296.

Pseudopalisading Necrosis is a Hallmark of Glioblastoma and where VEGF mRNA is Upregulated



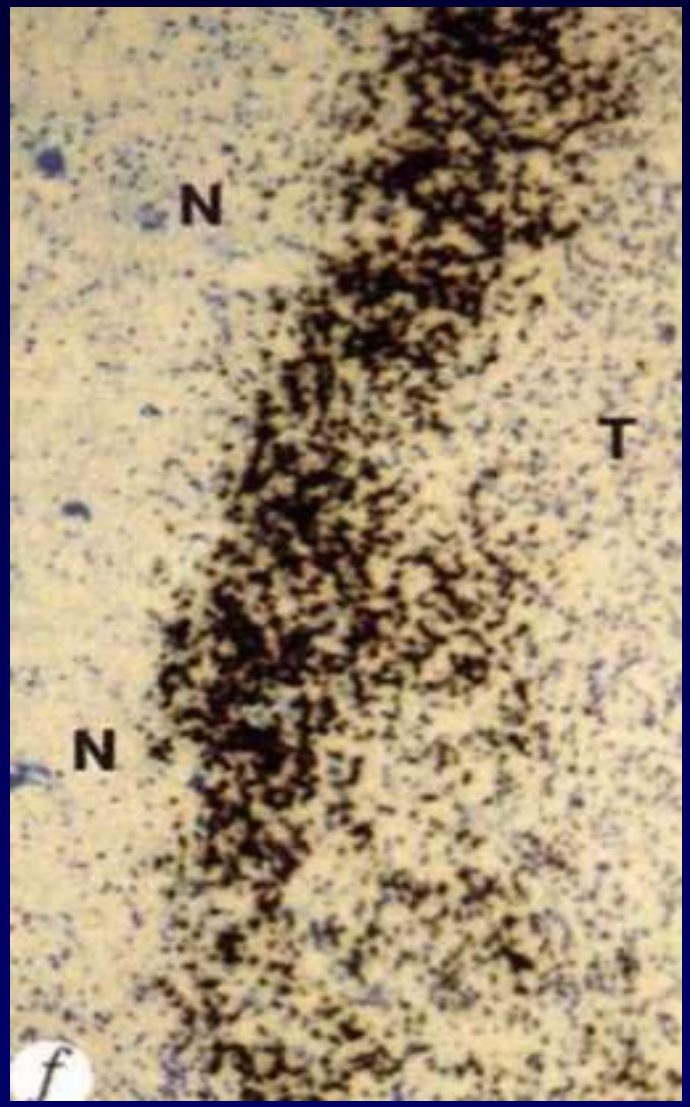


Plate KH, et al. *Nature* 1992;359:845-848.

Bevacizumab for Newly Diagnosed Glioblastoma

1. No survival benefit in the upfront treatment of glioblastoma

PRIMARY ENDPOINTS, AVAGLIO & RTOG 0825				
	AVAGLIO		RTOG 0825	
Regimen	Bev/TMZ/RT	TMZ/RT	Bev/TMZ/RT	TMZ/RT
PFS	10.6 months	6.2 months	10.3 months	7.3 months
	HR 0.64, p<0.0001		HR 0.79, p=0.07	
OS	16.8 months	16.7 months	15.7 months	16.1 months
	HR 0.88, p=0.0987		HR 1.13, p=0.21	
Sources: AVAglio: Wick, Abstract 2002, ASCO 2013; RTOG 0825: Gilbert, Abstract 1, ASCO 2013.				

2. There may be benefit in specialized population of patients with newly diagnosed glioblastoma (i.e. large unresectable tumor, molecular genetics, etc.)

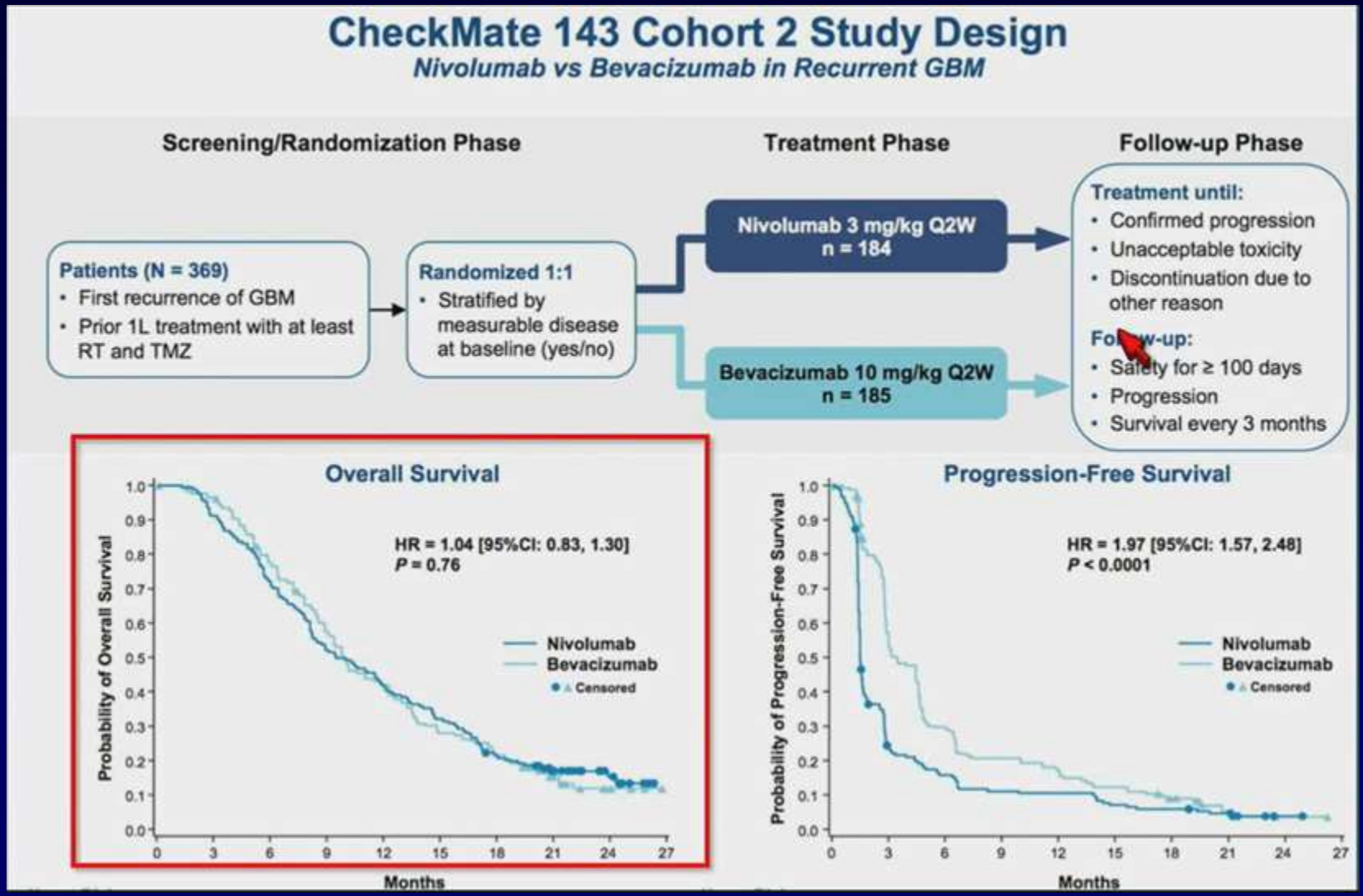
Targeted Therapies for Various Types of Common Malignancies versus Malignant Brain Tumor (www.cancer.gov/about-cancer/treatment)

Lung Cancer	Breast Cancer	Colon Cancer	Brain Cancer
Afatinib	Abemaciclib	Bevacizumab	Bevacizumab
Bevacizumab	Ado-Trastuzumab Emtansine	Cetuximab	
Ceritinib	Everolimus	Panitumumab	
Crizotinib	Lapatinib	Regorafenib	
Dabrafenib	Neratinib	Zvi-Aflibercept	
Erlotinib	Olaparib		
Gefitinib	Palbociclib		
Osimertinib	Pertuzumab		
Trametinib	Ribociclib		
	Trastuzumab		

Checkpoint Inhibitors: Therapeutic Indications

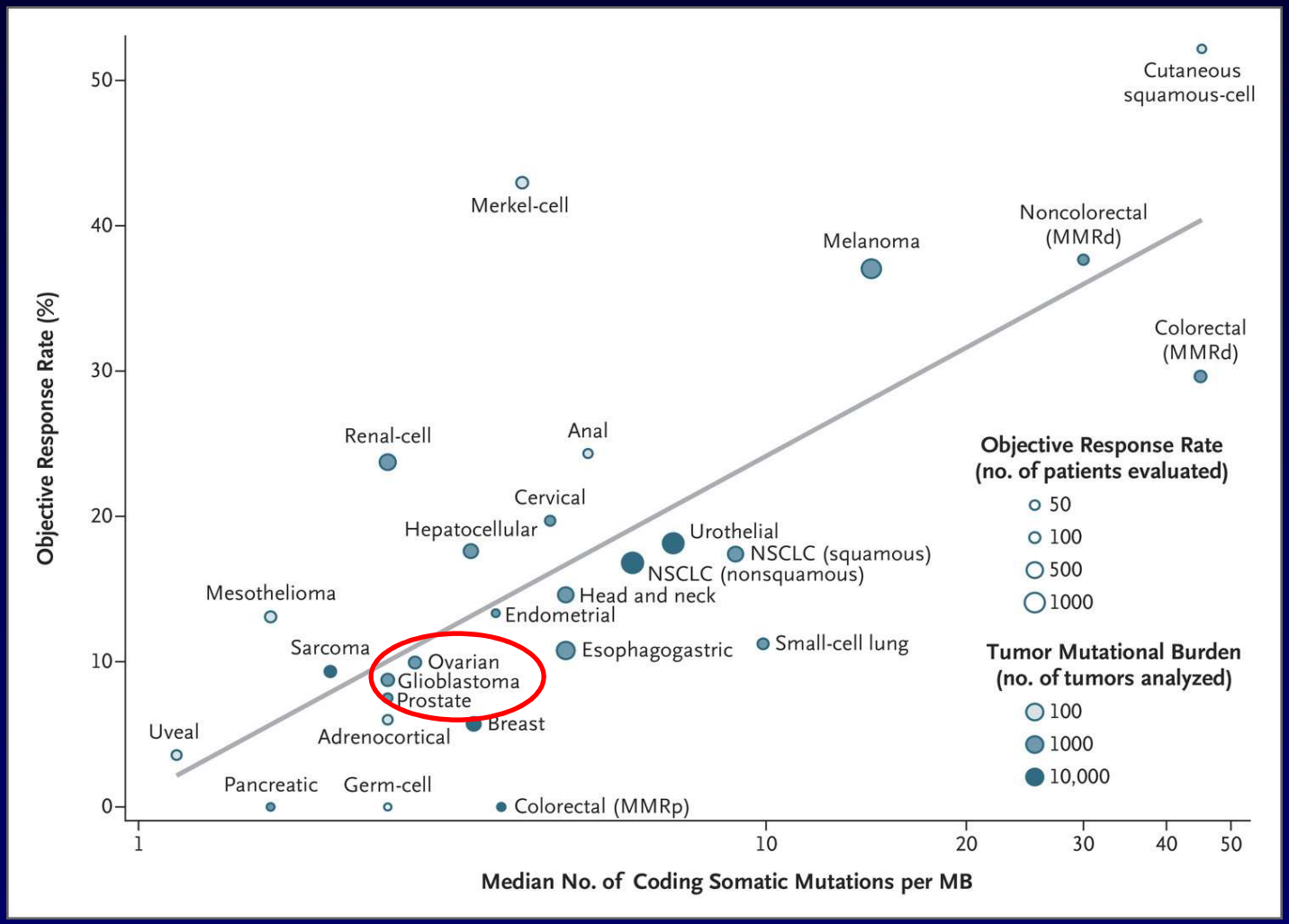
Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
Metastatic Melanoma	Metastatic NSCLC	Advanced Melanoma	Urothelial Cancer	Urothelial Cancer	Merkel Cell Cacrinoma
Adjuvant for Melanoma	Renal Cell Carcinoma	Metastatic NSCLC		NSCLC	Urothelial Cancer
Renal Cell Carcinoma	Hodgkin's Lymphoma	Renal Cell Carcinoma			
	Squamous H&N Cancer	Hodgkin's Lymphoma			
	Urothelial Cancer	PMBCL (Lymphoma)			
		Urothelial Cancer			
		MSI-H Cancer			
		Gastric Cancer			
		Cervical Cancer			

Nivolumab Failed to Improve Overall Survival of Patients with Recurrent Glioblastoma



Uhm J. Highlights of the Day Session 1, ASCO June 3, 2018.

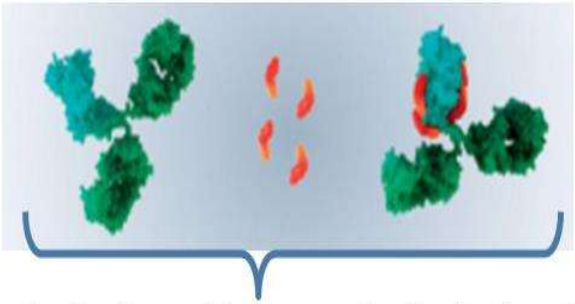
Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types



Yarchoan M et al. *N Engl J Med* 2017;377:2500-2501.

The NEW ENGLAND JOURNAL of MEDICINE

Depatux-M (ABT-414) is a Monoclonal Antibody Drug Conjugate (ADC) Directed Against EGFR

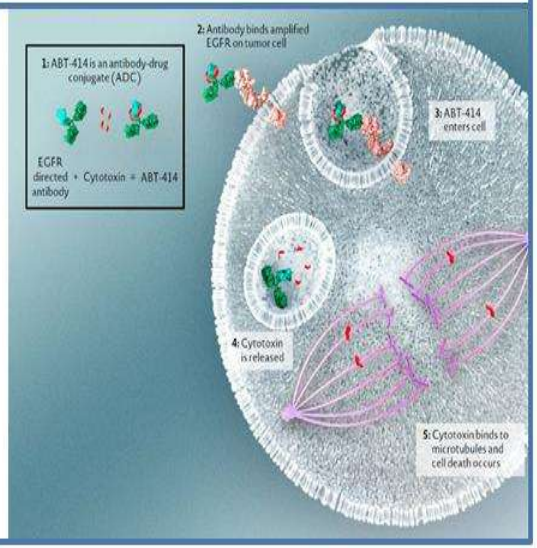


Antibody (ABT-806) + **Toxin (MMAF)** = **Antibody Drug Conjugate (Depatux-M)**

Depatux-M is an **antibody-drug conjugate (ADC),** comprised of an antibody that ***selectively targets activated EGFR*** and a cytotoxin that is **only released inside the *tumor* cell**

REF's: Gan HK, et al. *Cancer Res.* 2012;72(12):2924–2930, Doronina SO, et al. *Bioconjug Chem.* 2006;17(1):114-124, Trail PA. *Antibodies.* 2013;2:113-129.

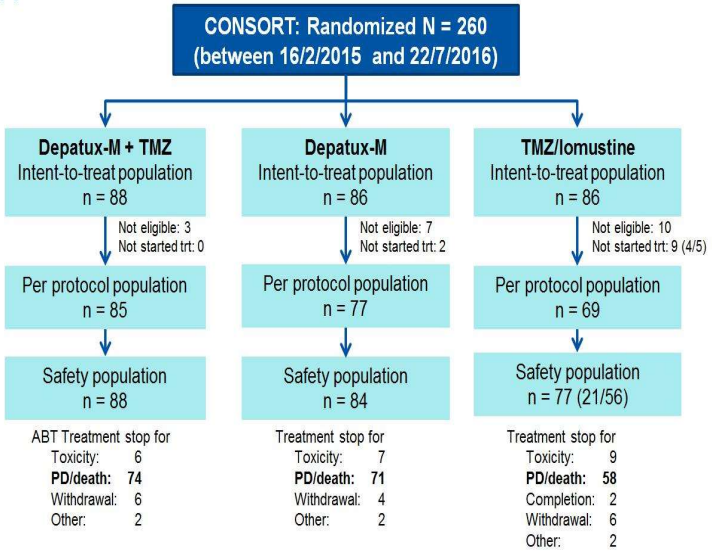
- EGFR amplification (~50% of GBM) leads to ***preferential exposure of a unique epitope*** of the EGFR protein that binds Depatux-M
- Unlike other EGFR directed therapies, there is **limited binding to EGFR in normal tissue** such as skin and other epithelial tissue.
- Depatux-M uses ***activated*** **EGFR** only as a target for **intracellular toxin delivery** and does not inhibit EGFR signaling; therefore, it can work in glioblastoma cells that are **resistant to classical EGFR inhibition**
- Phase I studies identified **EGFR amplification** as **biomarker for patient selection**



Disposition

Follow-up details at the time database lock (Oct 2018):

- Median follow-up for OS: 28.7 mo
- PD or died: 251
- **Died: 237 (91%)**
- Lost to follow-up: 4

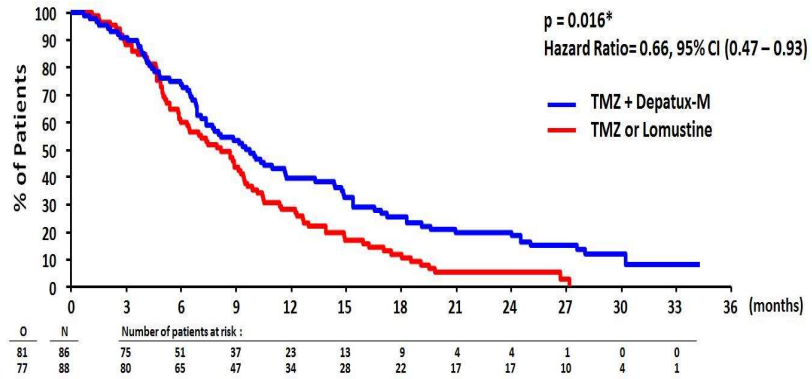


Toxicity: Hematological, Ocular

Hematology (worst grade)	TMZ+Depatux-M n = 88 n (%)		Depatux-M n = 84 n (%)		Lomustine n = 56 n (%)		Temozolomide n = 21 n (%)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
ANC	1 (1.1)				8 (14.3)	1 (1.8)	1 (4.8)	
Platelets	7 (8.0)	2 (2.3)	1 (1.2)		11 (19.6)	3 (5.4)	3 (14.3)	
WBC	2 (2.3)				9 (16.1)	2 (3.6)		

Ocular Toxicity (worst grade)	TMZ + Depatux-M n (%)	Depatux-M n (%)	Lomustine n = 56 n (%)	TMZ n = 21 n (%)
grade 0	13 (14.8)	22 (26.2)	51 (91.1)	21 (100.0)
grade 1	18 (20.5)	9 (10.7)	2 (3.6)	0
grade 2	29 (33.0)	32 (38.1)	3 (5.4)	0
grade 3	**27 (30.7)**	**20 (23.8)**	0 (0.0)	0
grade 4	**1 (1.1)**	**1 (1.2)**	0 (0.0)	0

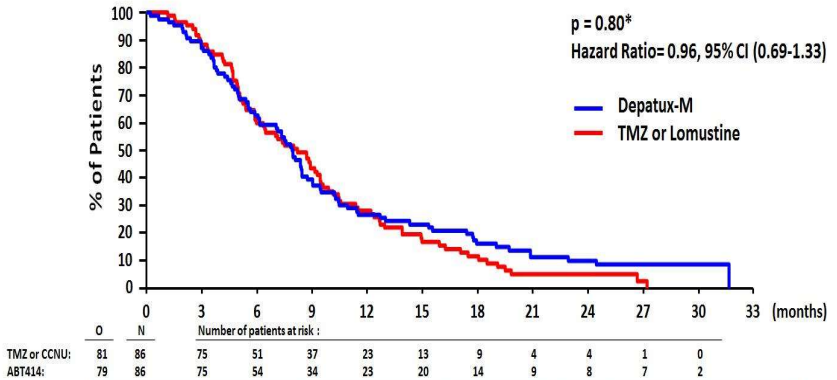
OS with 24+ months follow up:
Comparison TMZ+Depatux-M vs TMZ or Lomustine



Treatment	Patients	Observed Events	Median (95% CI) Months	% at 12 Months (95% CI)	% at 24 Months (95% CI)
TMZ or Lom	86	81	8.2 (5.9, 9.5)	28.2 (19.1, 37.9)	5.2 (1.7, 11.7)
TMZ+Depatux	88	77	9.6 (7.4, 11.8)	39.7 (29.4, 49.7)	19.8 (12.2, 28.8)

*Stratified log-rank test by stratification factors at randomization.

OS with 24+ months follow-up
Comparison of OS Depatux-M vs TMZ or Lomustine



Treatment	Patients	Observed Events	Median (95% CI) Months	% at 12 Months (95% CI)	% at 24 Months (95% CI)
TMZ or Lom	86	81	8.2 (5.9, 9.5)	28.2 (19.1, 37.9)	5.2 (1.7, 11.7)
Depatux-M	86	79	7.9 (6.1, 8.7)	26.7 (17.9, 36.4)	10.0 (4.8, 17.6)

*Stratified log-rank test by stratification factors at randomization.

Depatux-M in Recurrent EGFR ampl Glioblastoma

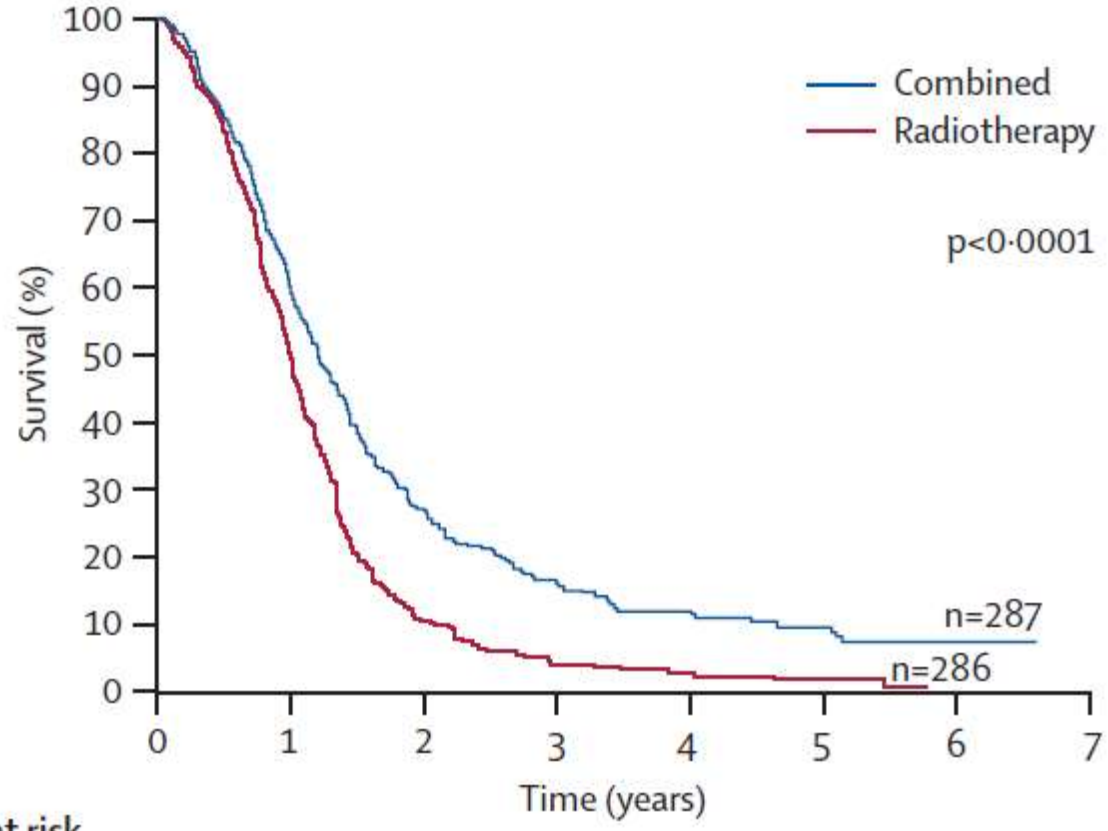
- Two phase I trial expansion cohorts demonstrated activity:
  - Depatux M monotherapy: ORR 6.8%, **6-mo PFS 29%** (n = 66)
  - Depatux M in combination with TMZ: ORR 14.3%, **6-mo PFS 25%** (n = 60)
- Dose limiting toxicity: **keratopathy**
- Two randomized trials to establish clinical activity:
  - INTELLANCE-2 study: in recurrent glioblastoma: conducted by EORTC, primary endpoint overall survival
    - Report 2017 SNO: 199 survival events
  - INTELLANCE-1 study: in newly diagnosed glioblastoma, conducted by NRG foundation

Lassman et al, *Neuro Oncol.* 2018 doi: 10.1093/neuonc/noy091. van den Bent et al, *Cancer Chemother Pharmacol.* 2017;80:1209-1217.

FDA-Approved Treatments for Malignant Glioma

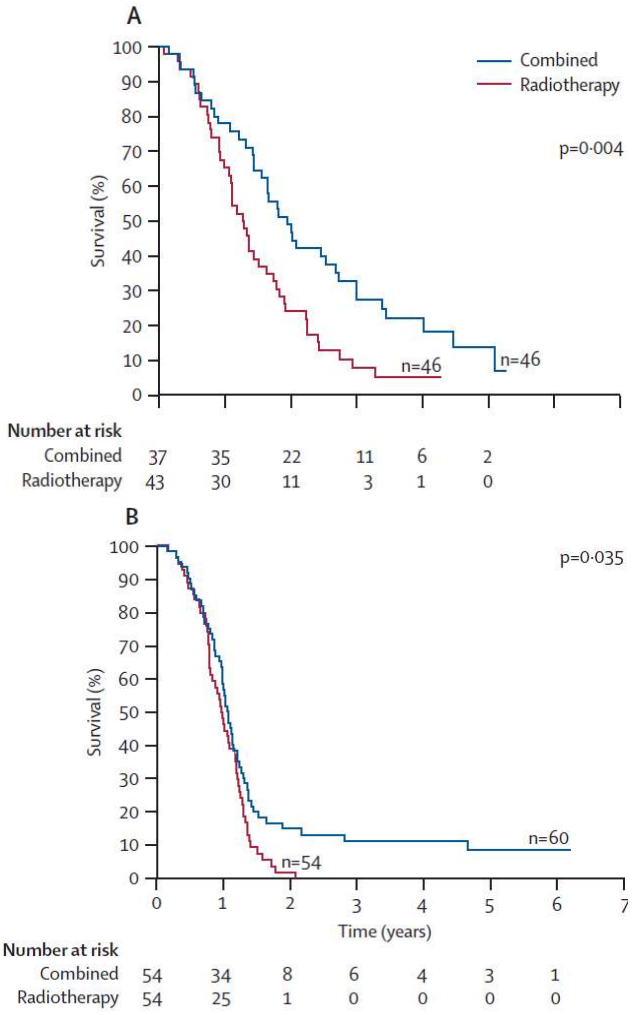
- June 14, 1996: Carmustine wafer for recurrent glioblastoma
- January 12, 1999: Temozolomide for anaplastic astrocytoma
- February 25, 2003: Carmustine wafer for newly diagnosed glioblastoma
- **March 15, 2005: Temozolomide for newly diagnosed glioblastoma**
- May 5, 2009: Bevacizumab for progressive glioblastoma (provisional approval)
- April 15, 2011: Tumor Treating Fields for recurrent glioblastoma
- **October 5, 2015: Tumor Treating Fields for newly diagnosed glioblastoma**
- June 6, 2017: Aminolevulinic acid hydrochloride (5-ALA HCl)
- December 5, 2017: Bevacizumab for recurrent glioblastoma (full approval)

Temozolomide Has Proven Efficacy for Glioblastoma in Randomized Phase III Clinical Trial



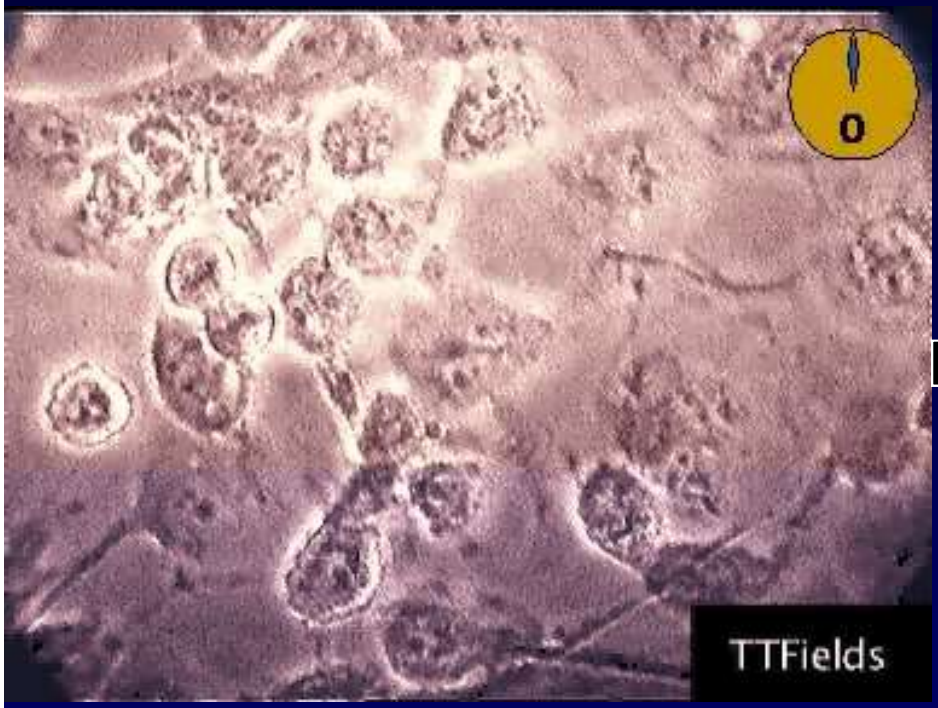
Number at risk

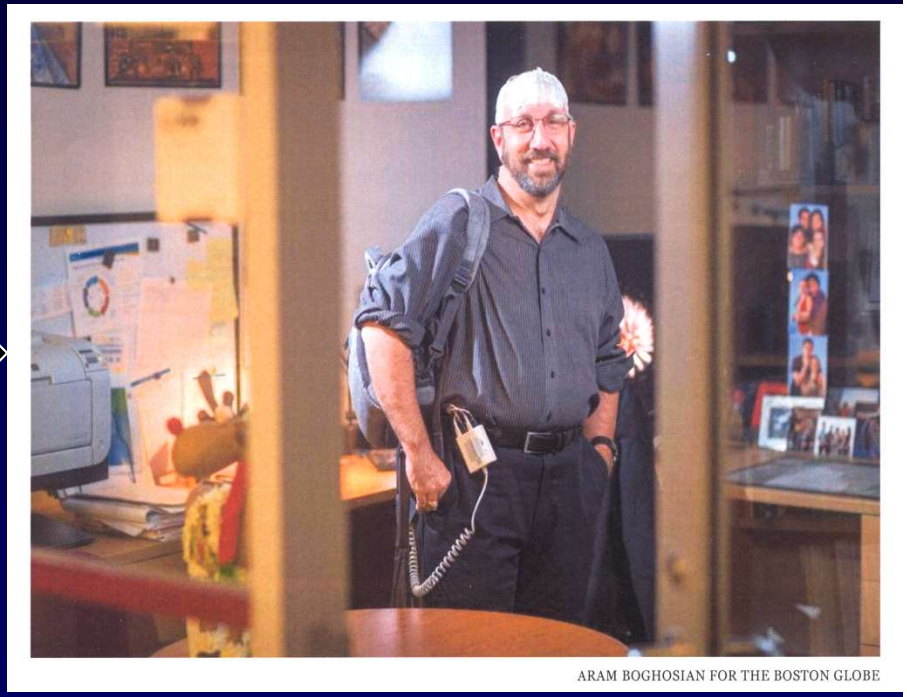
Combined	254	175	76	39	23	14	6
Radiotherapy	278	144	31	11	6	3	0



Stupp R, Hegi ME, Mason EP, et al. *Lancet Oncol* 2009;10:459-466.

NovoTTF-100A Alternating Electric Fields Therapy for Recurrent Glioblastoma





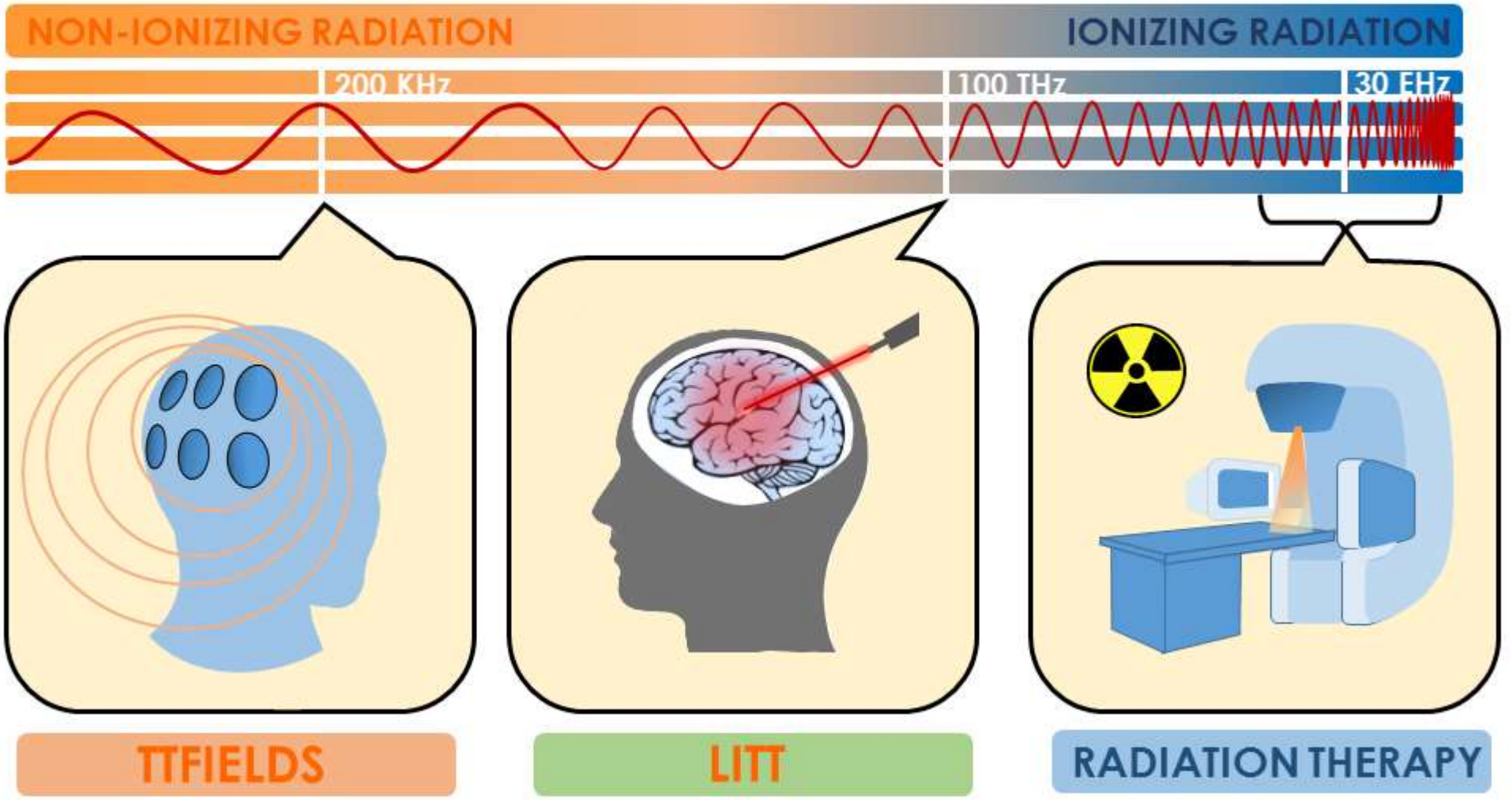
ARAM BOGHOSIAN FOR THE BOSTON GLOBE

Stupp R, Wong ET, Kanner AA, et al. *Eur J Cancer* 2012;48:2192-2202.

Fonkem E, Wong ET. *Exp Rev Neurother* 2012;12:895-899.

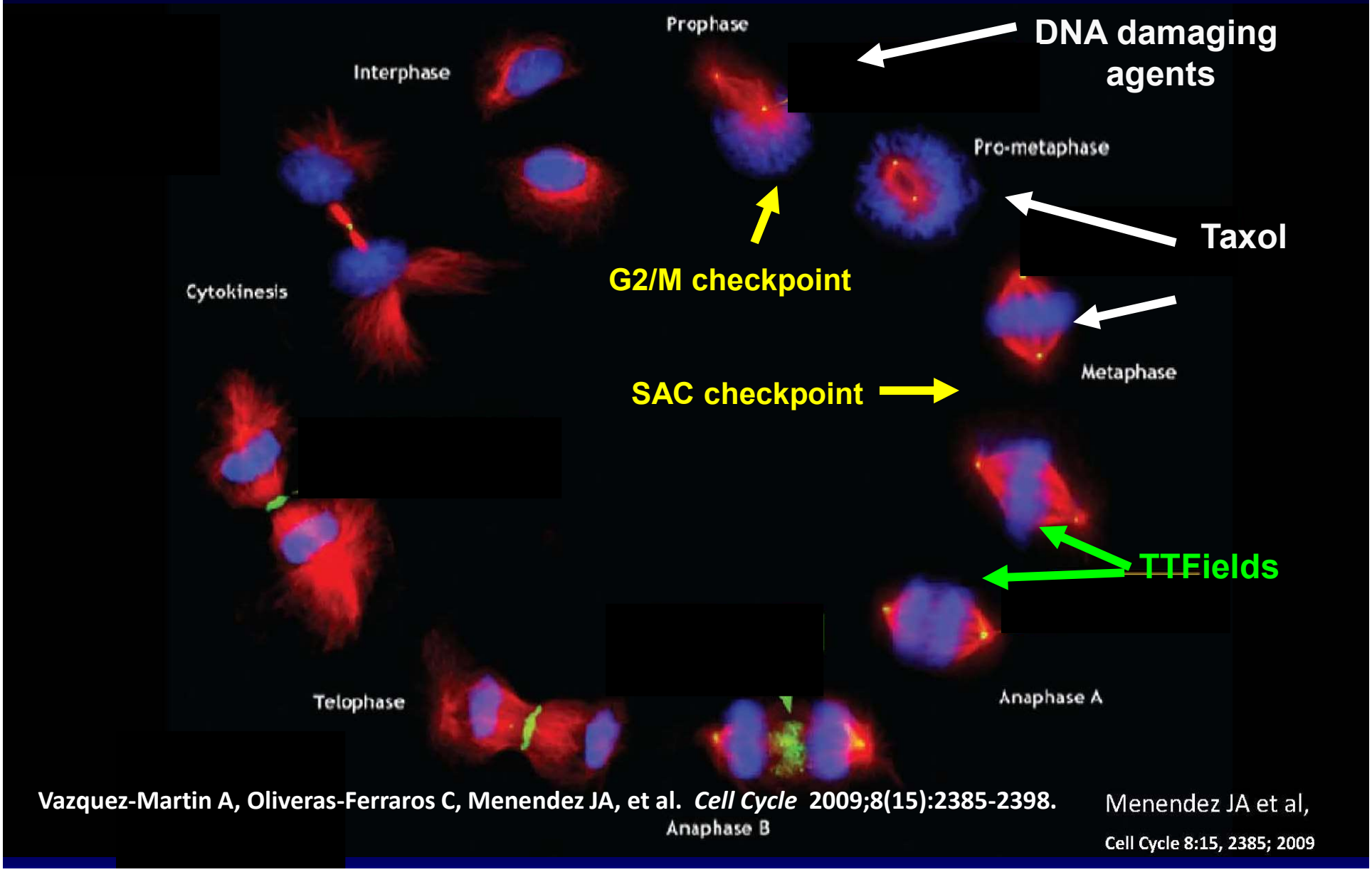
Boston Globe, December 27, 2014

Applications of the Electromagnetic Spectrum for Brain Tumors



Swanson KD, Lok E, Wong ET. Tumor treating electric fields for glioblastoma. In Brem S and Abdullah KG (Editors): Glioblastoma, Chapter 17, pp. 213-224, 2016.

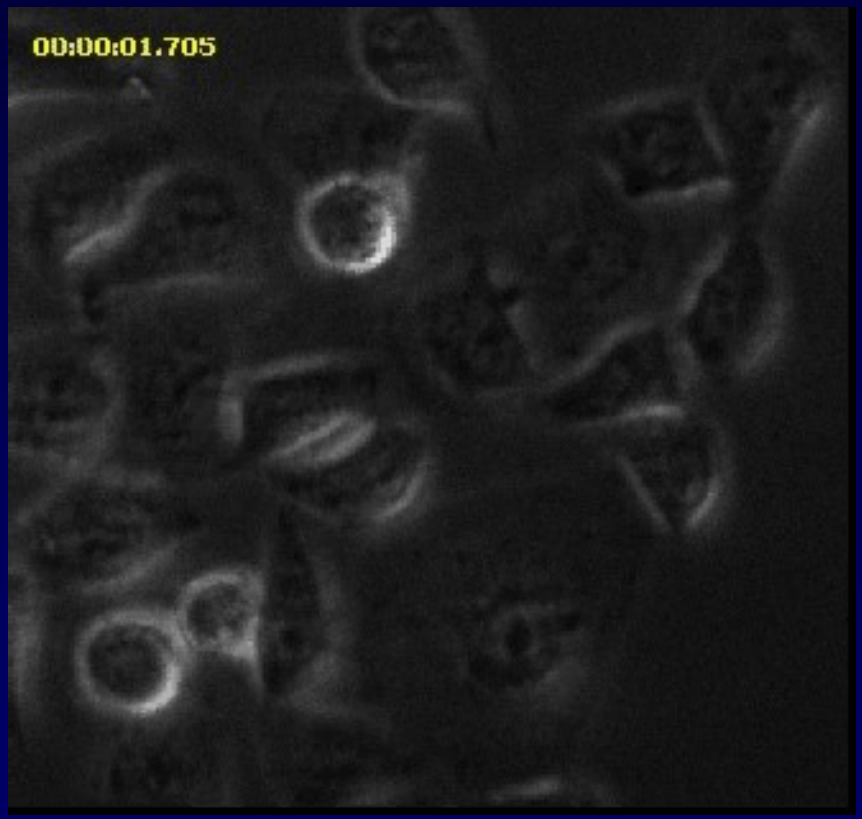
Tumor Treating Fields Appear to Affect Cells After DNA Damaging Agents and Spindle Poisons

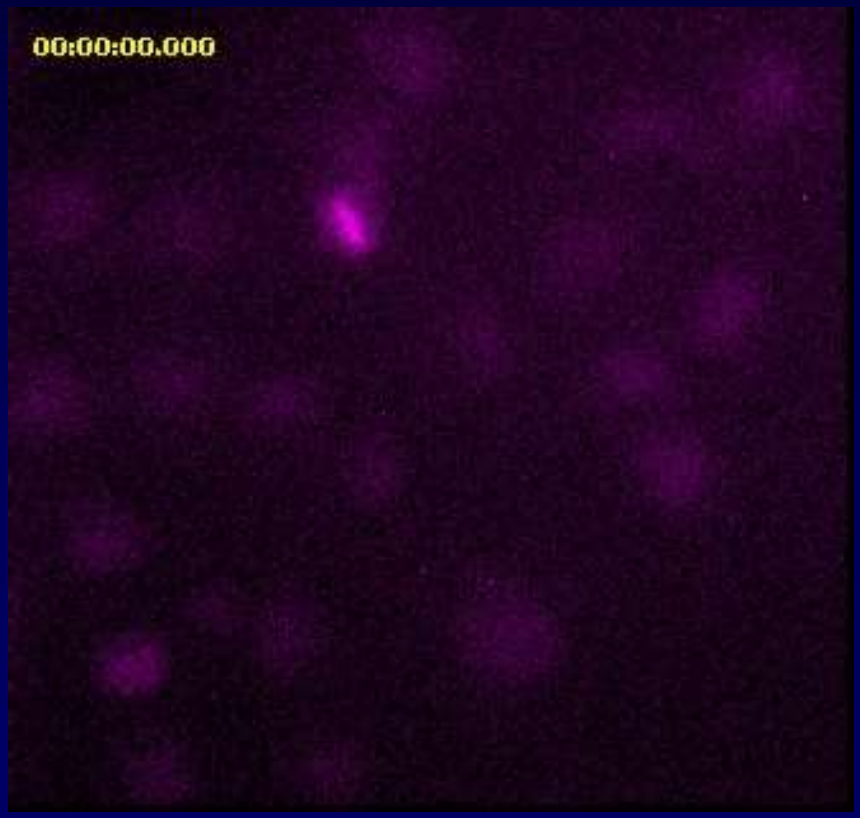


Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA, et al. *Cell Cycle* 2009;8(15):2385-2398.

Menendez JA et al,
Cell Cycle 8:15, 2385; 2009

Normal Mitosis

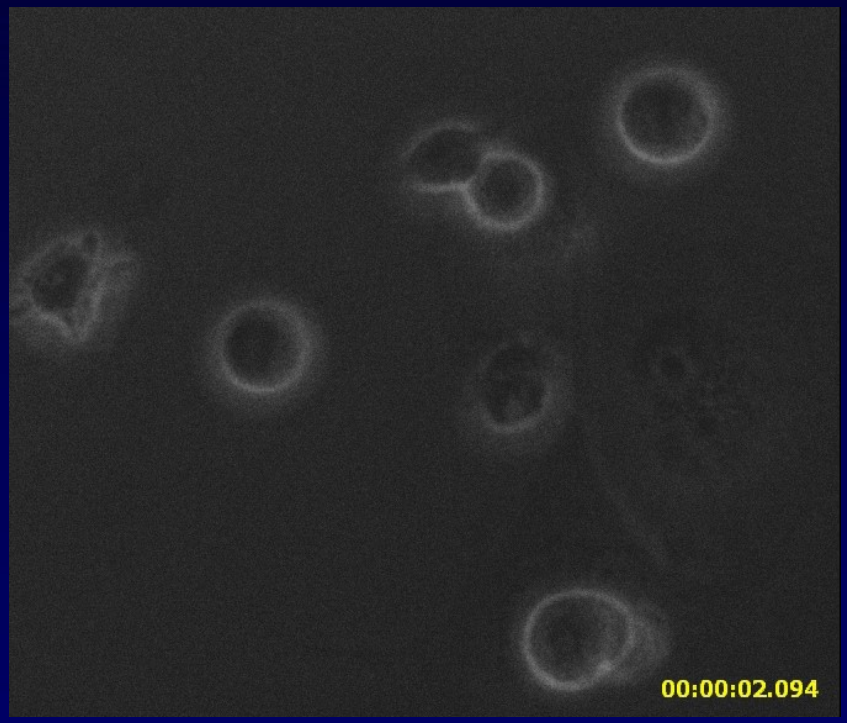




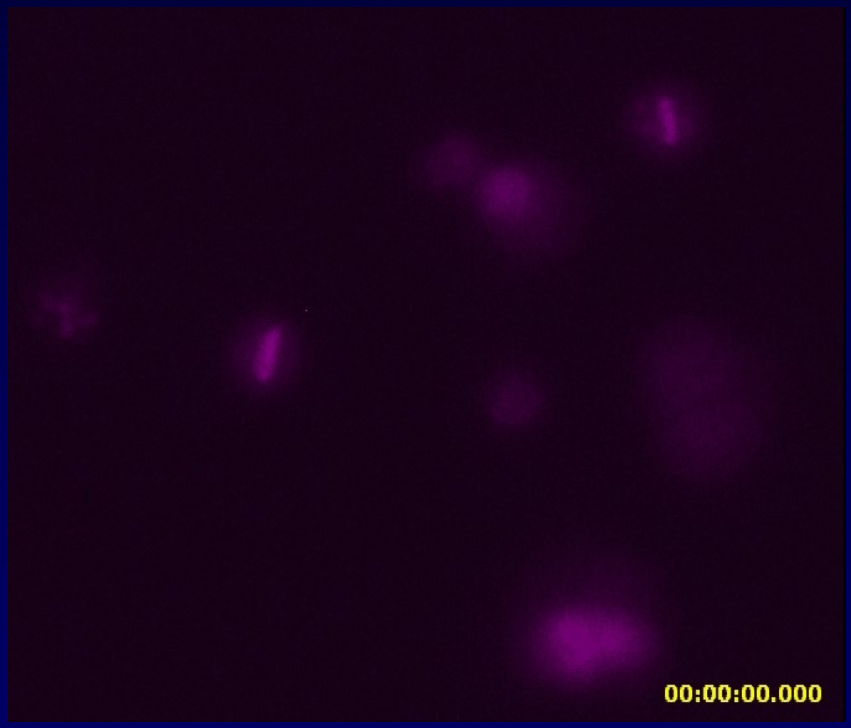
Phase Contrast

DNA (DRAQ5)

Tumor Treatment Fields Disrupt Cells During Transition from Metaphase to Anaphase

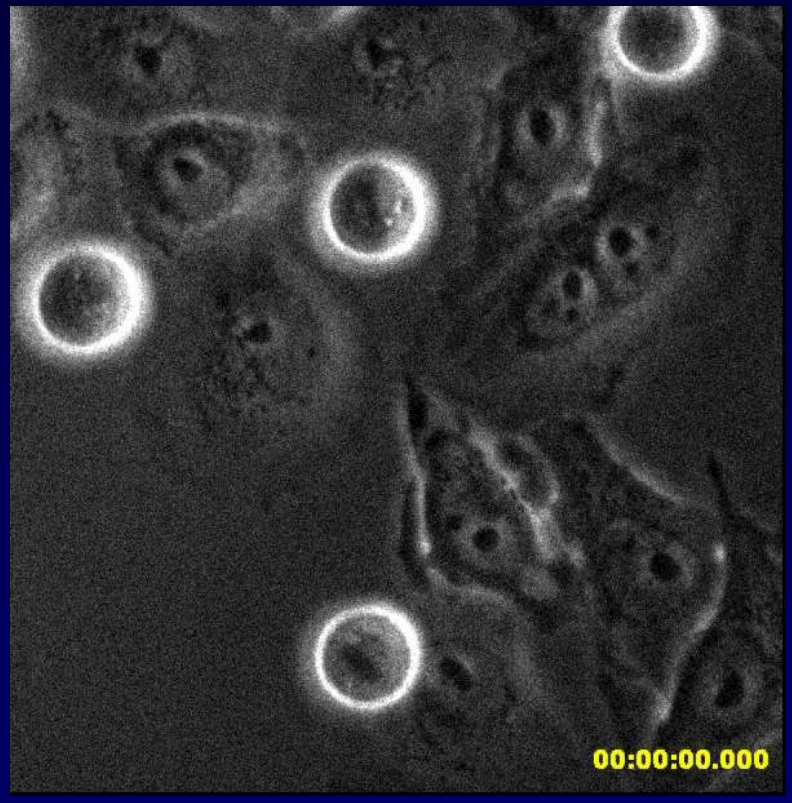


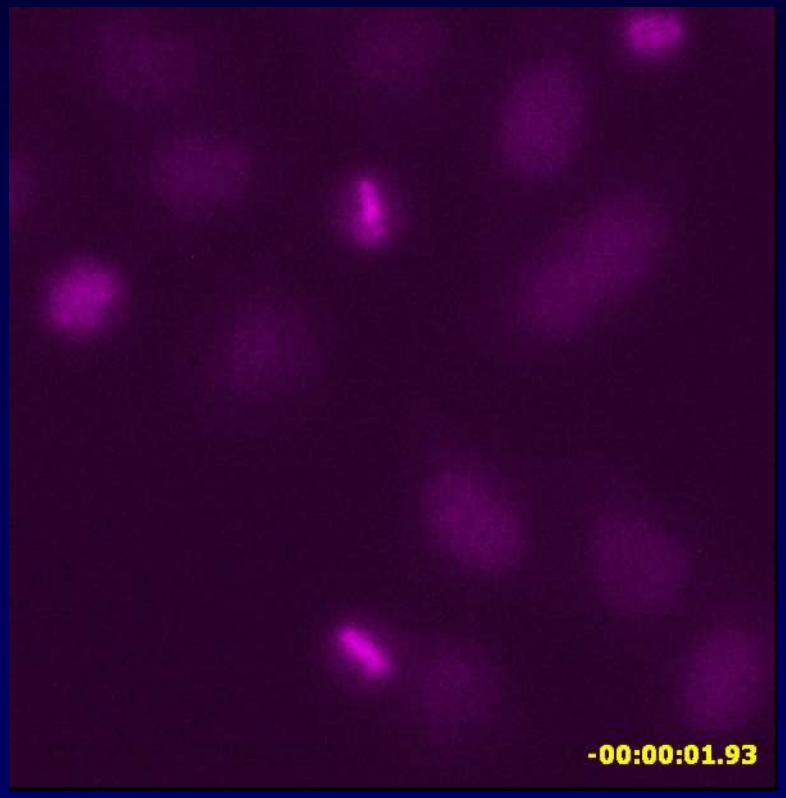
Phase Contrast



DNA (DRAQ5)

TTFields Perturb Cytokinesis





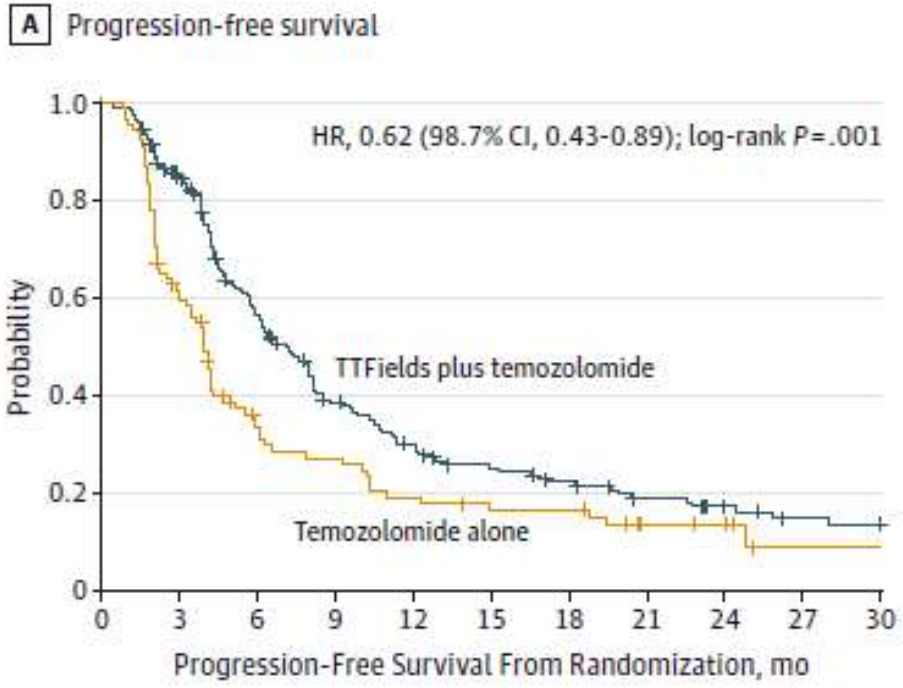
Phase Contrast

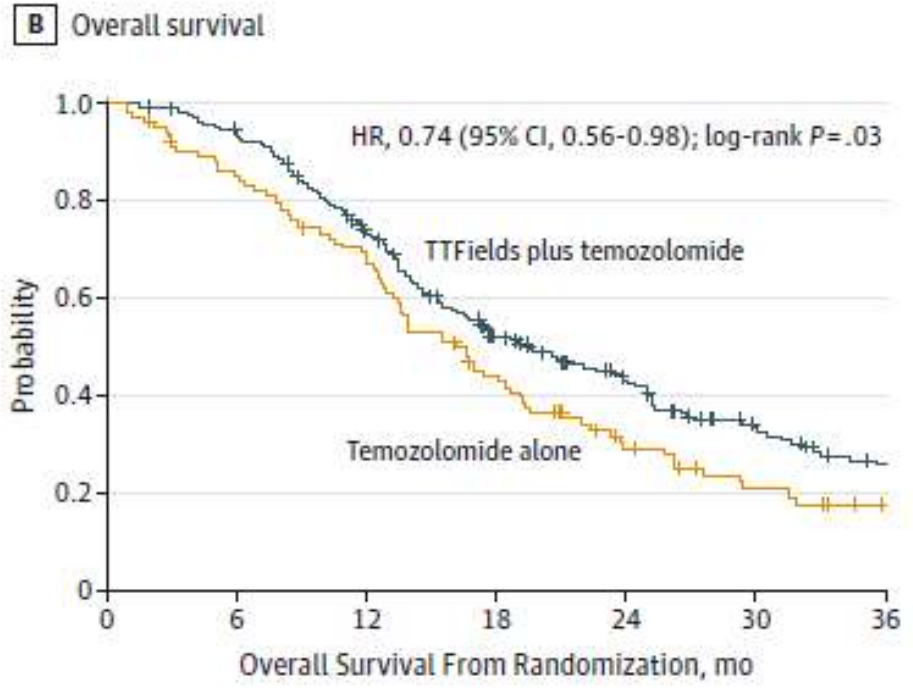
DNA (DRAQ5)

Maintenance TTFields Added to Radiotherapy and Temozolomide Improves Survival of Glioblastoma Patients

PFS: 7.1 vs 4.0 months

OS: 20.5 vs 15.6 months





PFS: progression free survival

OS: overall survival

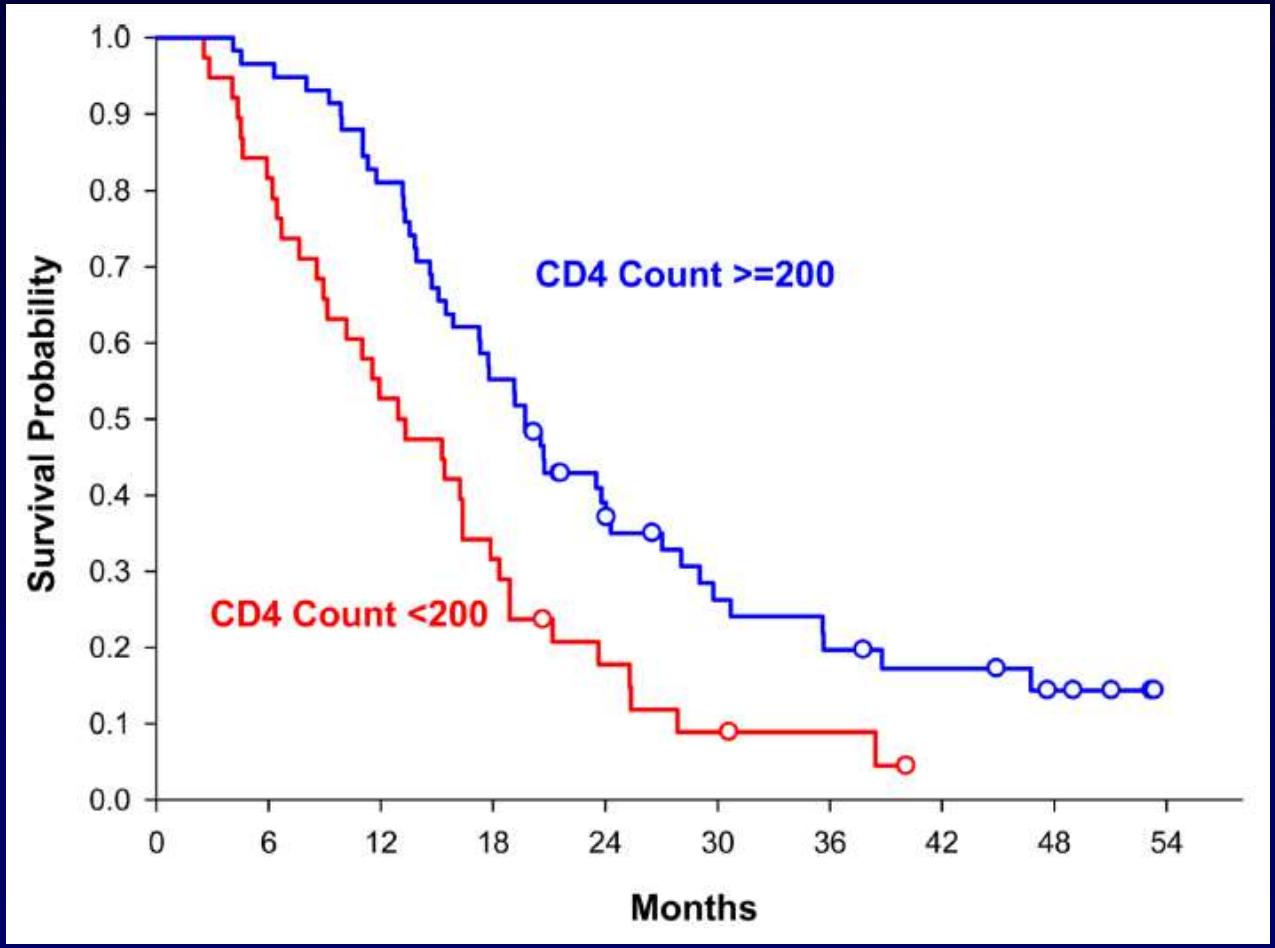
Stupp R, Taillibert S, Kanner AA, et al. *JAMA* 2017;314(23):2535-2543.

EF-14 Safety Analysis: Grade 3 or 4 Adverse Events in ≥2% of Patients

Safety Population	TTFields + TMZ (n=456) %		TMZ Alone (n=216) %	
System Organ Class	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	9	4	9	2
Leukopenia	2	0	<1	0
Lymphopenia	3	1	3	0
Neutropenia	2	1	1	<1
Thrombocytopenia	6	3	4	1
Gastrointestinal disorders	5	<1	3	<1
General disorders and administration site conditions	9	<1	6	0
Fatigue	4	0	3	0
Asthenia	3	0	1	0
Gait disturbance	2	0	1	0
Infections and infestations	7	<1	4	1
Procedural complications	5	0	3	0
Fall	2	0	1	0
Medical device site reaction	2	0	0	0

Stupp R, Tallibert S, Kanner AA, et al. *JAMA* 2015;314:2535-2543.
Stupp R, Idbaih A, Steinberg DM, et al. AACR Annual Meeting 2017, April 1-4, Washington, DC.

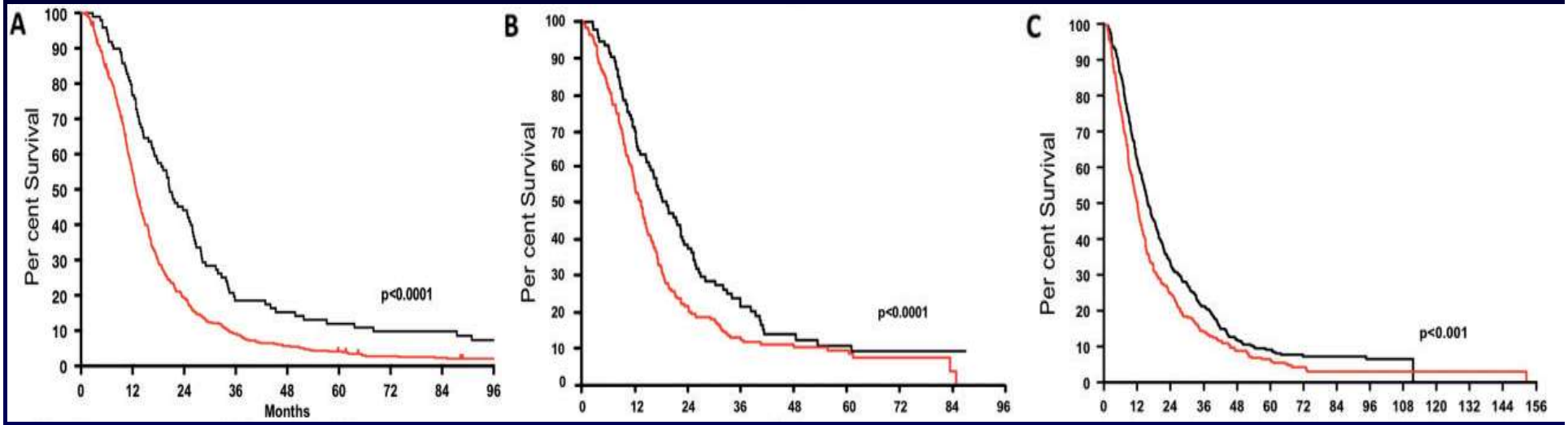
Absolute CD4 Lymphocyte Count is Prognostic for Newly Diagnosed Glioblastoma Patients



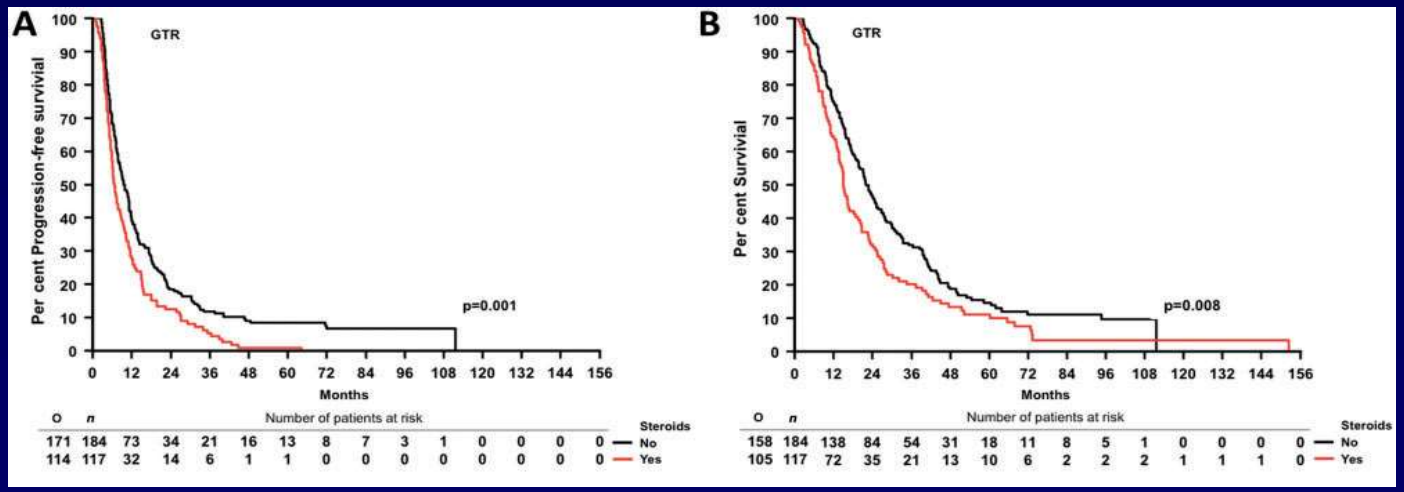
Grossman SA, Ye X, Lesser G, et al. *Clin Cancer Res* 2011;17:5473-5480.

Dexamethasone Compromises Survival of Glioblastoma Patients

MSKCC EORTC/NCIC GGN



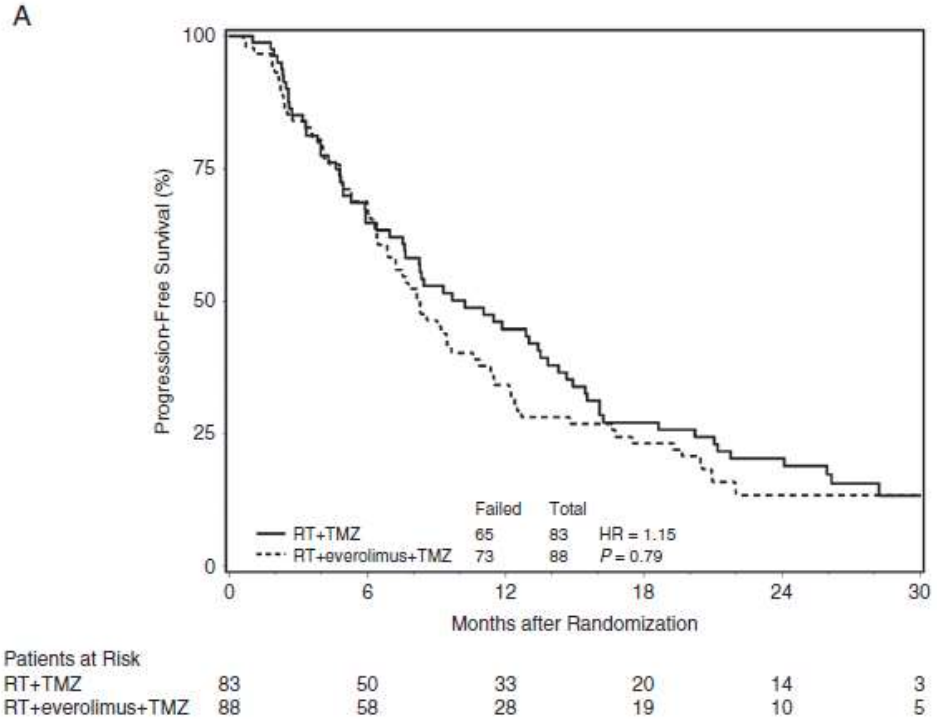
GGN (Gross Total Resection): PFS OS



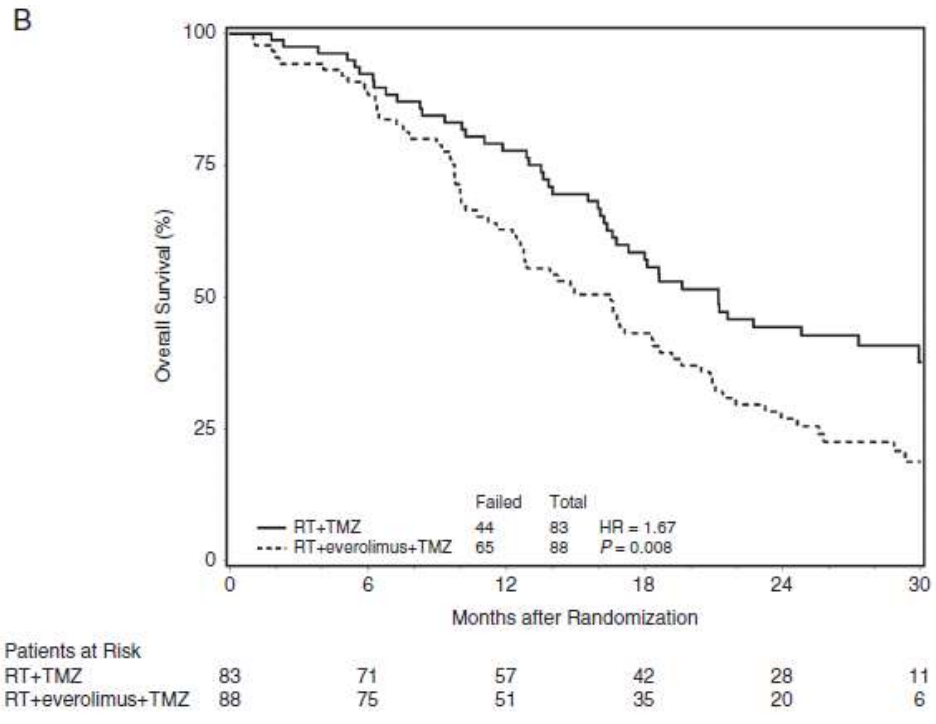
Pitter KL, Tamagno I, Alikhanyan K, et al. *Brain* 2016;139(5):1458-1471.

Immunosuppressant Everolimus Shortens Survival of Glioblastoma Patients

Progression Free Survival



Overall Survival



Chinnaiyan P, Won M, Wen PY, et al. *Neuro-Oncol* 2018;20(5):666-673.

Separate Package Inserts for Everolimus from Pharma

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor indicated for the treatment of:

- postmenopausal women negative breast cancer (exemestane after failur
- adults with progressive that is unresectable, loc effectiveness of AFINI tumors have not been e
- adults with advanced re with sunitinib or sorafe
- adults with renal angio not requiring immediat treatment of renal angi objective responses in follow-up of patients is
- adults and children ≥ 3 astrocytoma (SEGA) a therapeutic interventio resection. The effective change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated. (1.5)

----------DOSAGE AND ADMINISTRATION----------

Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

- 10 mg once daily with or without food. (2.1)

AFINITOR dose by approximately 50%. Subsequent dosing should be based on therapeutic drug monitoring (TDM). (2.4)

- If strong inducers of CYP3A4 are required, double the AFINITOR dose. Subsequent dosing should be based on TDM. (2.4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZORTRESS® (everolimus) safely and effectively. See full prescribing information for ZORTRESS.

ZORTRESS (everolimus) tablets for oral use.
Initial U.S. Approval: 2010

----------DOSAGE AND ADMINISTRATION----------

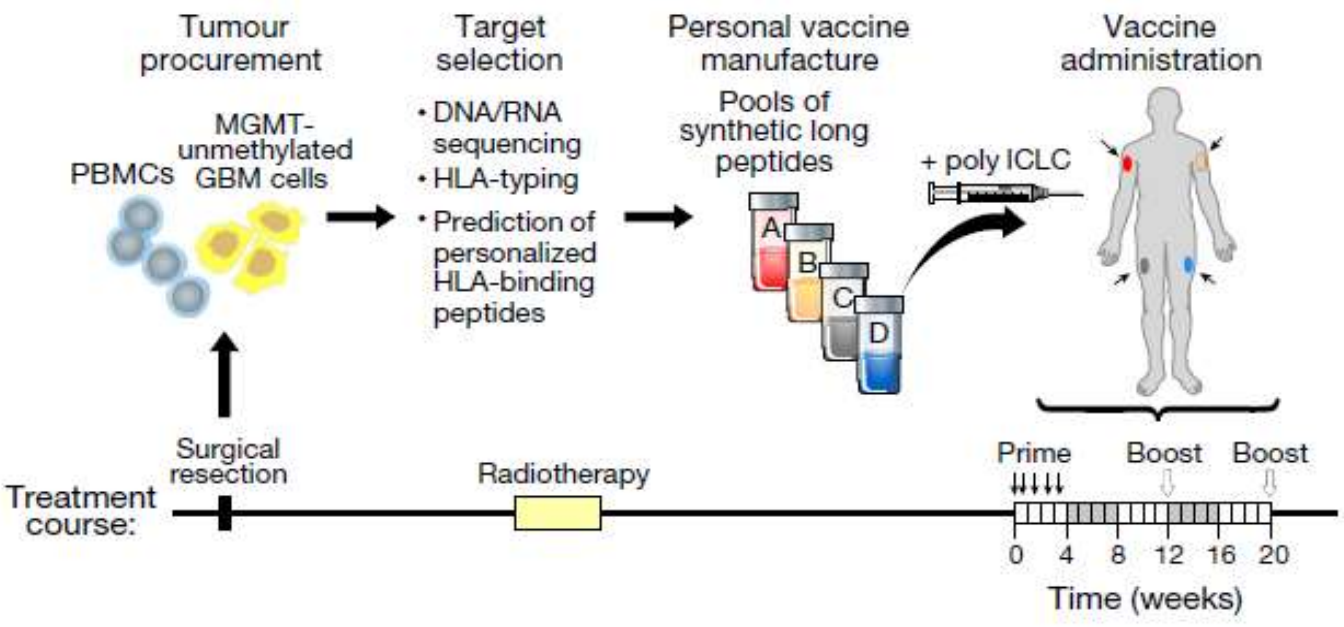
- Kidney transplantation: starting oral dose of 0.75 mg twice daily as soon as possible after transplantation. (2.1)
- Liver transplantation: starting oral dose of 1.0 mg twice daily starting 30 days after transplantation. (2.2)

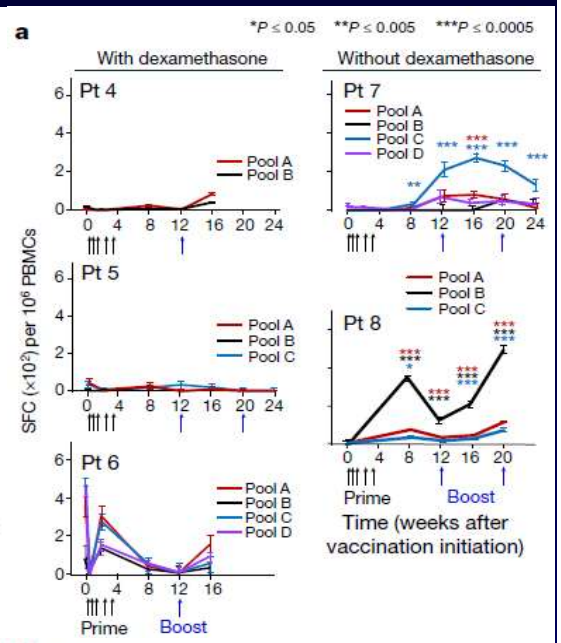
----------DOSAGE AND ADMINISTRATION----------

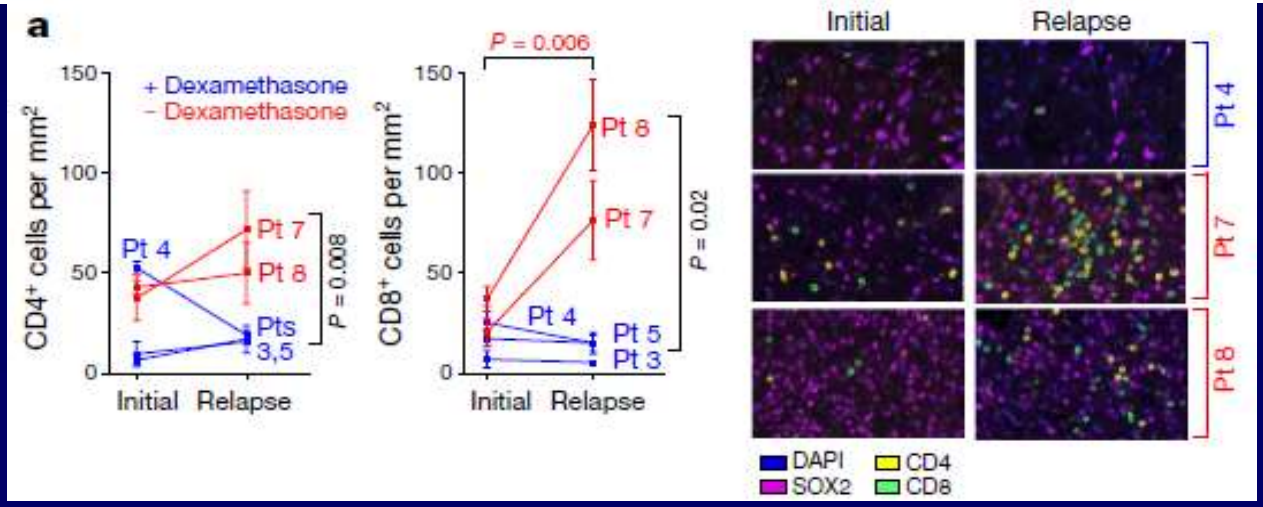
- Kidney transplantation: starting oral dose of 0.75 mg twice daily as soon as possible after transplantation. (2.1)
- Liver transplantation: starting oral dose of 1.0 mg twice daily starting 30

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021560s006lbl.pdf

Dexamethasone Attentuates Personalized Neoantigen Vaccines in Glioblastoma





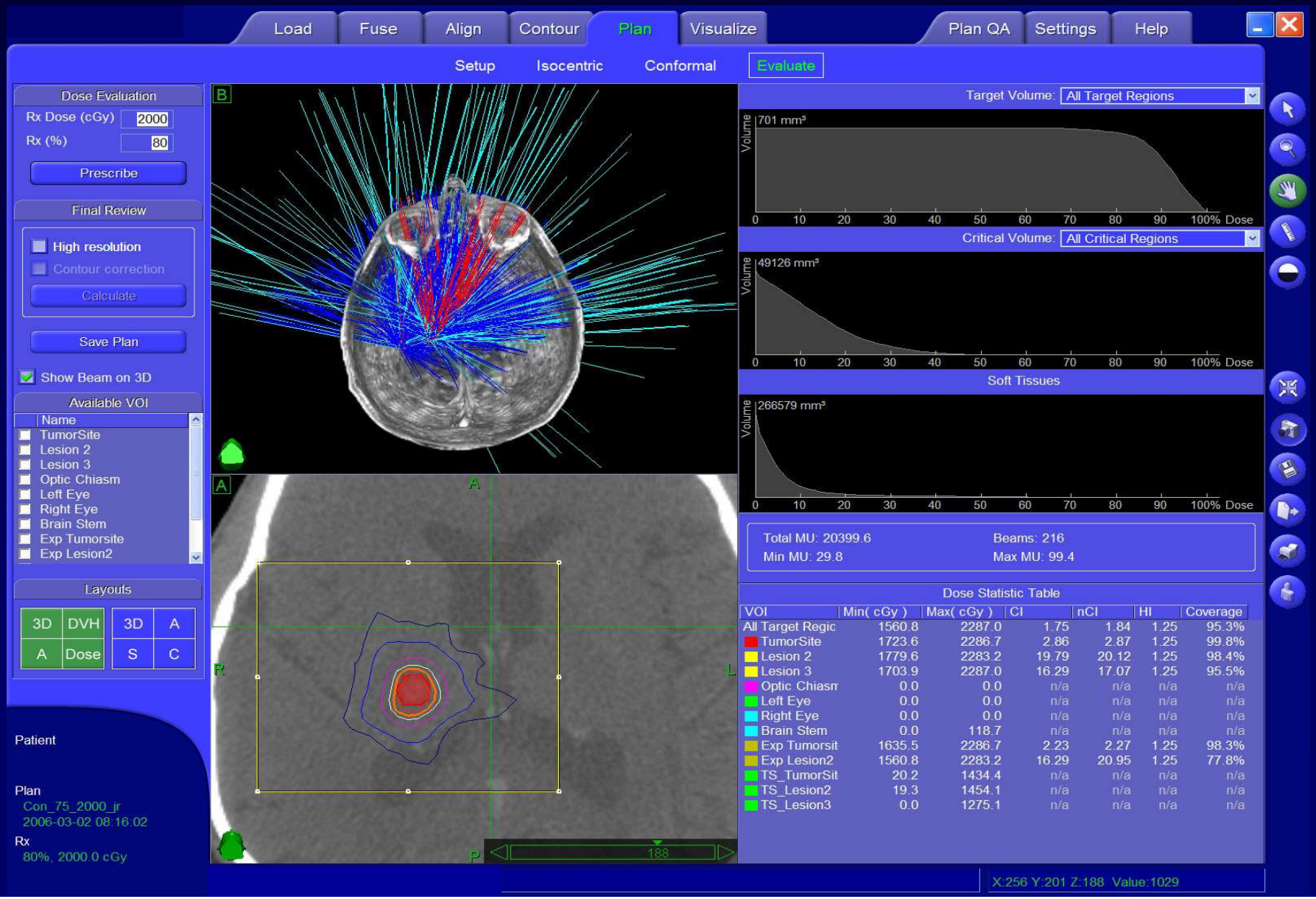


Keskin DB, Anandappa AJ, Sun J, et al. *Nature* 2019;565(5):1458-1471.

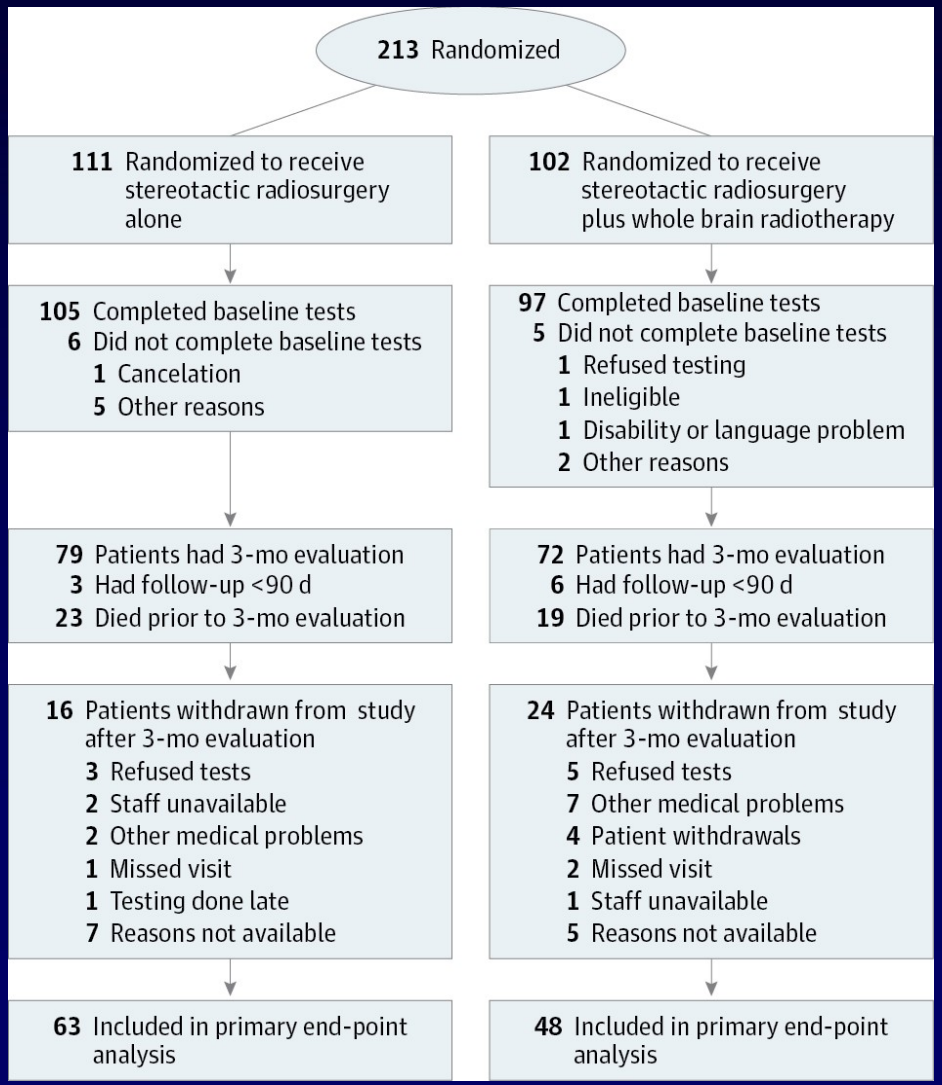
Update on the Management of Malignant Gliomas

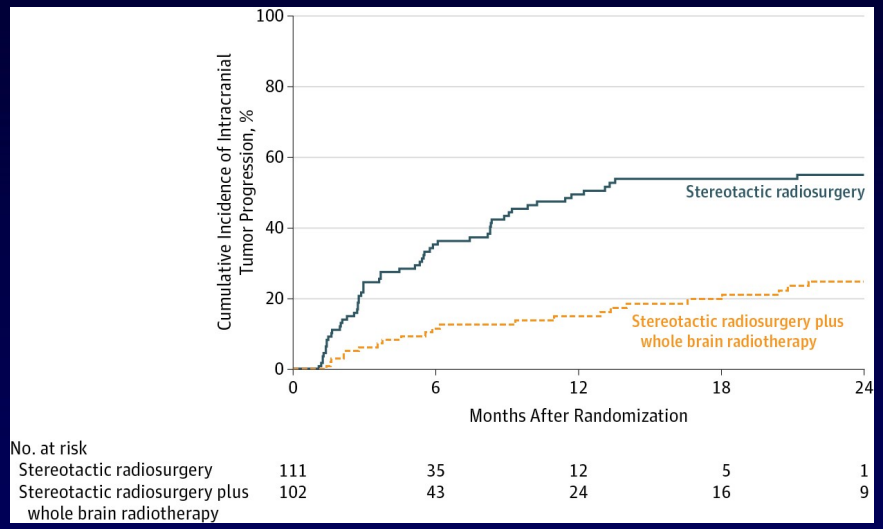
- Temozolomide added to radiation has been the standard-of-care for newly diagnosed glioblastoma since 2005.
- Adjuvant Tumor Treating Fields therapy was approved by the FDA in 2015 for newly diagnosed glioblastoma.
- Bevacizumab received final approval by the FDA for use in recurrent glioblastoma in 2017.
- Targeted therapy or checkpoint inhibitors offer no survival advantage to glioblastoma patients.
- Dexamethasone interferes with treatments against glioblastoma.

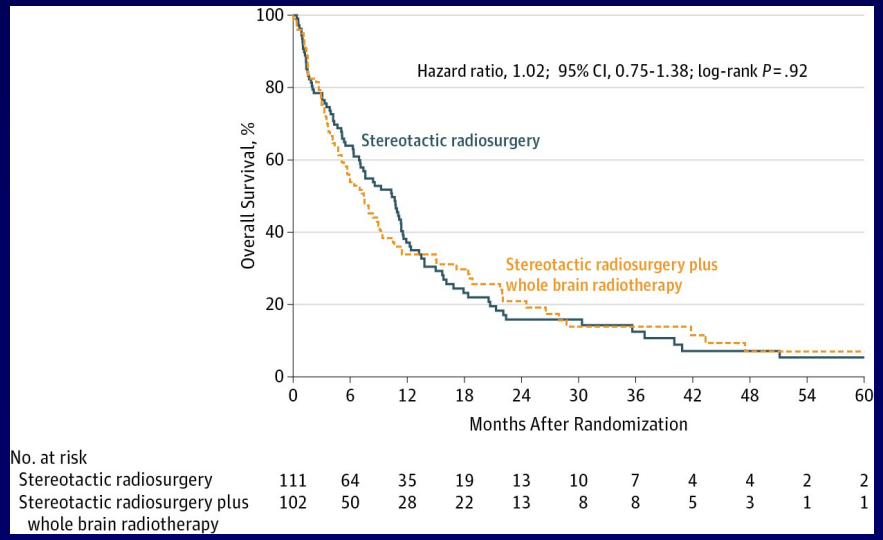
Stereotactic Radiosurgery for Brain Metastasis



SRS vs SRS + WBXT for Patients with 1-3 Brain Metastases (60-70% NSCLC)







Brown PD, et al. *JAMA* 2016;316(4):401-409.

SRS vs SRS + WBXT for Patients with 1-3 Brain Metastases (60-70% NSCLC)

Table 2. Patients Who Experienced Cognitive Deterioration by 3 Months and Difference Between Groups

	No. (%) of Participants			
	SRS Alone (n = 63)	SRS Plus WBRT (n = 48)	Mean Difference, % (95% CI)	*P* Value[a]
Change from baseline[b]				
HVLT-R				
Immediate recall				
Deterioration	5 (8.2)	14 (30.4)	22.2 (5.4 to 39.1)	.004
No deterioration	56 (91.8)	32 (69.6)		
Delayed recall				
Deterioration	12 (19.7)	24 (51.1)	31.4 (12.1 to 50.7)	<.001
No deterioration	49 (80.3)	23 (48.9)		
Recognition				
Deterioration	14 (22.6)	19 (40.4)	17.8 (−1.5 to 37.2)	.06
No deterioration	48 (77.4)	28 (59.6)		
TMT-A time to complete				
Deterioration	10 (16.7)	14 (30.4)	13.8 (−4.4 to 32.0)	.11
No deterioration	50 (83.3)	32 (69.6)		
TMT-B time to complete				
Deterioration	11 (19.0)	16 (37.2)	18.2 (−1.4 to 37.9)	.07
No deterioration	47 (81.0)	27 (62.8)		
COWAT total				
Deterioration	1 (1.9)	8 (18.6)	16.7 (2.4 to 31.0)	.01
No deterioration	52 (98.1)	35 (81.4)		
GPS total seconds				
Deterioration	17 (29.3)	21 (47.7)	18.4 (−2.4 to 39.3)	.07
No deterioration	41 (70.7)	23 (52.3)		
Outcome for cognitive progression at 3 mo				
Stable	23 (36.5)	4 (8.3)	−28.2 (−44.2 to −12.2)	<.001
Progression	40 (63.5)	44 (91.7)		

Abbreviations: COWAT, Controlled Oral Word Association Test; GPS, Grooved Pegboard Test; HVLT-R, Hopkins Verbal Learning Test-Revised; SRS, stereotactic radiosurgery; TMT, Trail Making Test; WBRT, whole brain radiotherapy.

[a] By Fisher exact test.

[b] Cognitive deterioration was defined as a decline of 1 SD in score from baseline.

Brown PD, et al. *JAMA* 2016;316(4):401-409.

Erlotinib for Brain Metastasis from Oncogene-Addicted NSCLC (EGFR Mutated)

Drug	Trial	*N*	icRR (%)	icDOR (months)	icPFS (months)
Erlotinib	Retrospective (29)	17	82	NA	11.7
	Ph II (30)	8	58.4	NA	10.1
Gefitinib	Ph II (32)	41	88	NA	14.5
	Retrospective (34)	14	43	7.7	9.1
Afatinib	Pooled analysis (37)	81	21[a]	NA	8.2[a]
Icotinib[b]	Ph III (38)	85	65	NA	10.0
AZD3759	Ph I (28)	18	83	NA	NA
Osimertinib	AURA + AURA2 (49, 50)	128	54[c]	NR	1 year: 56%
	AURA3 (51)	116	70[d]	8.9[d]	11.7
	FLAURA (17)	128	66	NA	NR

icDOR, intracranial duration of response; icRR, intracranial response rate; icPFS, intracranial progression-free survival; NA, not available; NR, not reached.

[a]*Systemic RR and progression-free survival (PFS).*

[b]*Patients should have at least 3 metastatic brain lesions.*

[c]*In 50 evaluable patients.*

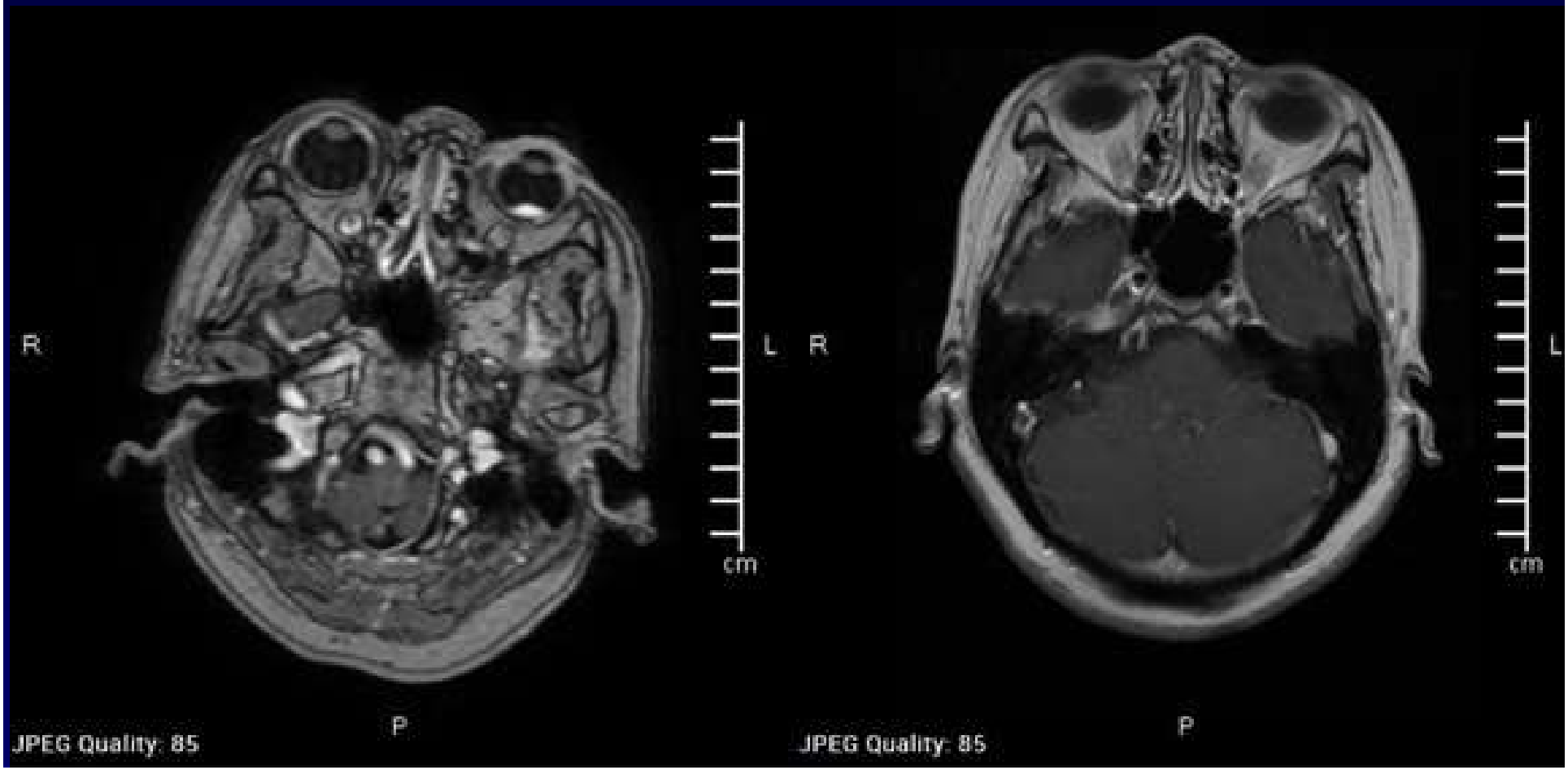
[d]*In 30 evaluable patients with osimertinib.*

Remon J, Besse B. *Front Oncol* 2018;8:88.

Erlotinib Induced Response in NSCLC Retinal Metastasis

Baseline

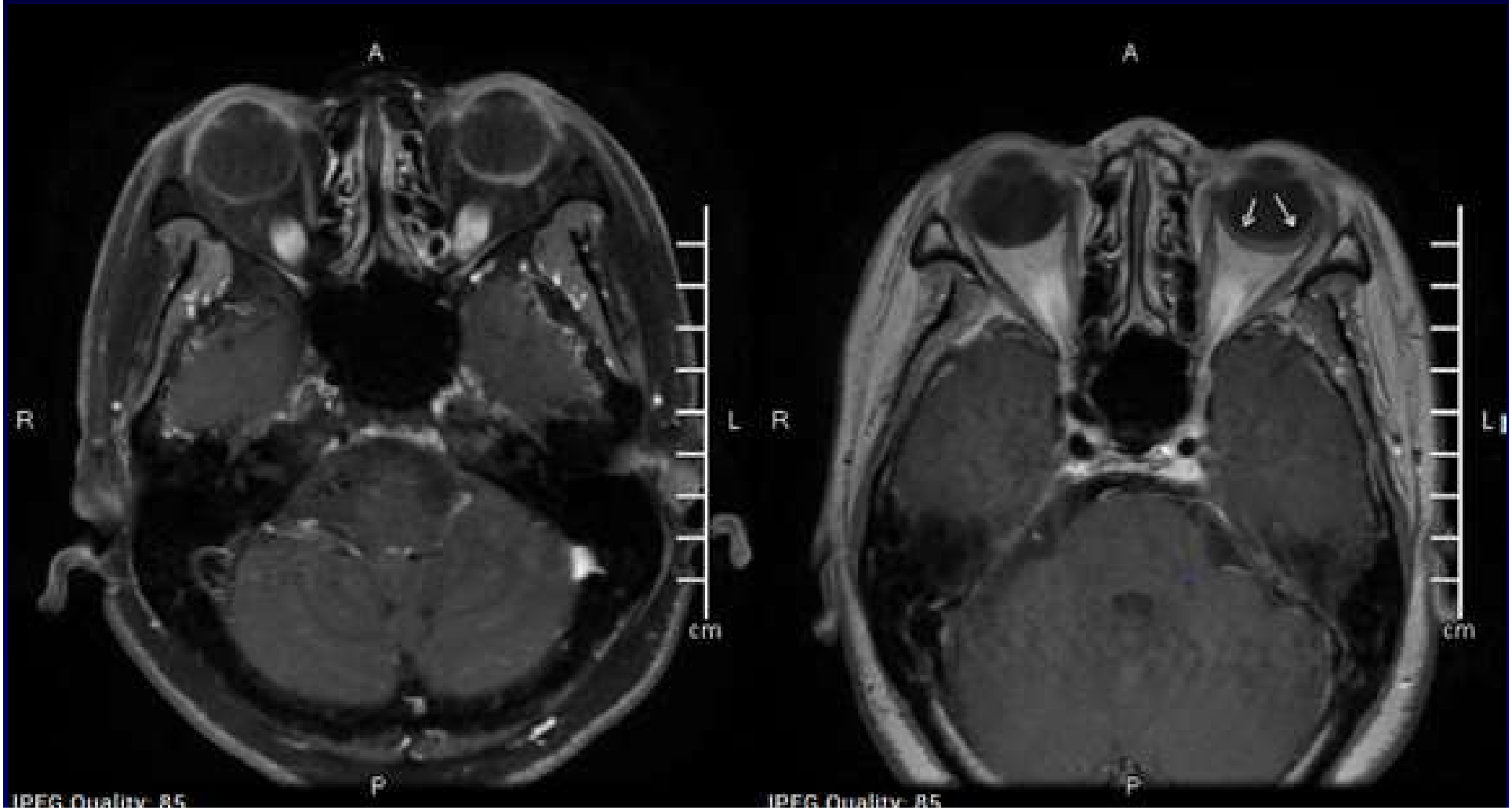
2 Months Later



Erlotinib Induced Response in NSCLC Retinal Metastasis

16 Months Later

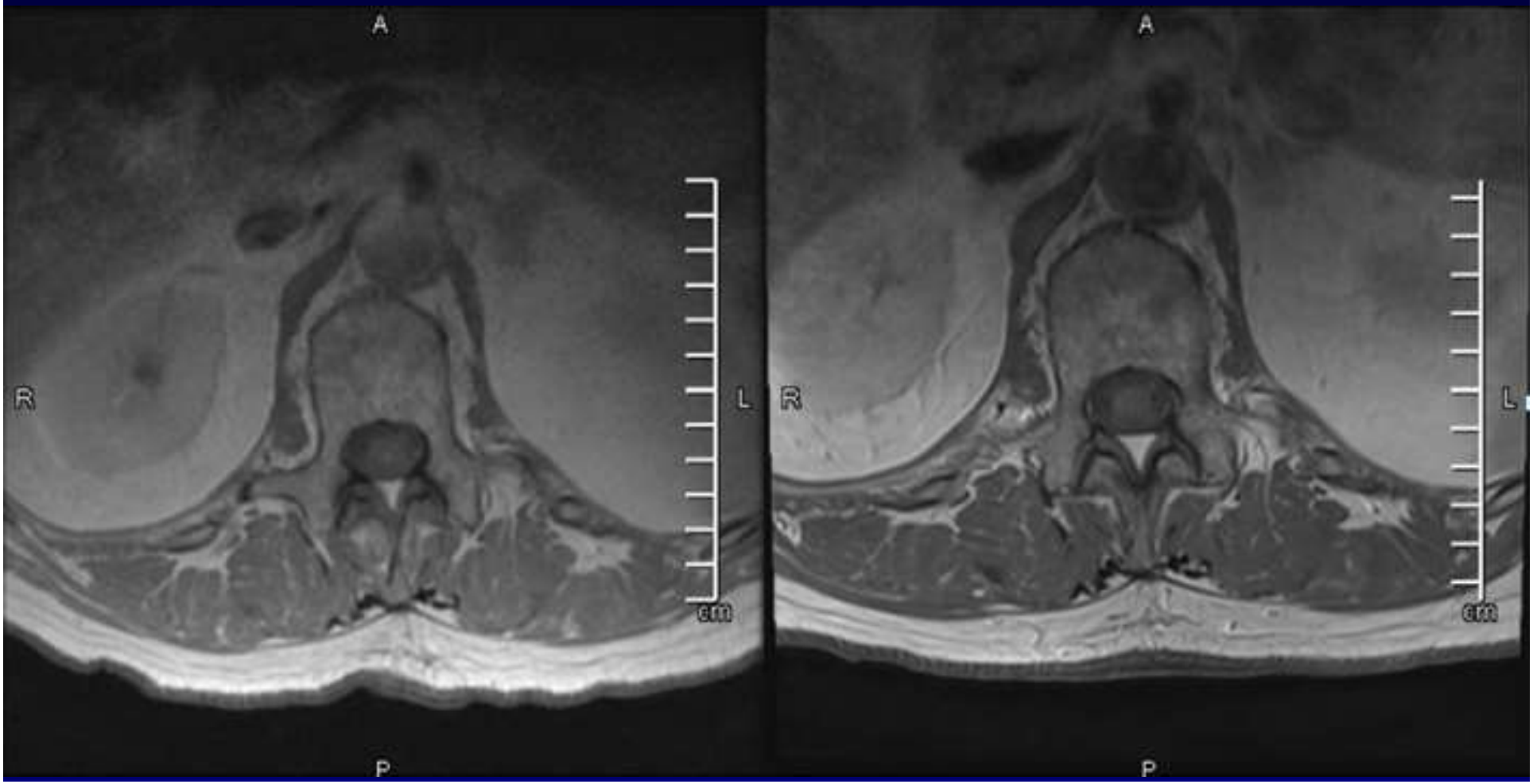
19 Months Later



Osimeltinib Induced Response in NSCLC Intramedullary Spinal Cord Metastasis

Baseline

6 Months Later



Osimertinib for Brain Metastasis from Oncogene-Addicted NSCLC (ALK Rearranged)

Drug	Trial (reference)	Brain M1	Measurable Brain M1	icRR (%)	icTTP (months)	s/ic PFS (months)	icDOR (monthss)
Crizotinib	PROFILE 1005 + 1007 pooled. ALK-naïve (previous CT) (68)	275	22/18[b]	18/33[b]	7.0/13.2	NA	26.4,/NR[b]
	PROFILE 1014. Ph III ALK-naïve (70)	79	79	85[c]	15.7	sPFS: 9	NA
Ceritinib	ASCEND 5. Ph III Crizotinib + CT resistant (76)	133	17	35 72.7	NA	sPFS: 4.4	6.9 16.6
	ASCEND 4. Ph III ALK-naïve (64)	121	22	62	NA	sPFS: 10.7	NA
	ASCEND 3. Ph II ALK TKI-naïve[a] (75)	49	13	39.4	NA	sPFS: 10.8	9.2
	ASCEND 2. Ph II Crizotinib-resistant (74)	100	33	63	NA	sPFS: 5.4	8.2,
	ASCEND 1. Ph I Naïve and pretreated (73)	94	36	61[d]	NA	NA	11.1[d]
Alectinib	Pooled analysis of ph II. Crizotinib resistant (85)	136	50	64	9.2	NA	10.8
	ALUR ph II. Crizotinib and CT resistant (86, 87)	76	40	54	NA	sPFS: 9.6	17.3
	ALEX. Ph III. ALK TKI-naïve (65, 72)	122	21	81	NA	sPFS: 25.7	
Lorlatinib	Ph I in *ALK*-positive (11% crizotinib-naïve) (90)	41	19	42	NA	sPFS: 9.6	12.4
	Ph I in *ROS1*-positive (90)	12	5	60	NA	sPFS: 7.0	12.0
	Ph II in *ALK/ROS1*-positive (91)						
	ALK TKI treatment-naïve	8	8	75	NA	NR	NA
	Prior crizotinib only and crizotinib ± 1-2 CT	37	37	68	NA	NR	NA
	No-crizotinib TKI ± CT	12	12	42	NA	sPFS: 5.5	NA
	2-3 ALK TKI ± CT	83	83	48	NA	sPFS: 6.9	NA
	ROS1-positive any prior line	25	25	56	NA	sPFS:9.6	NA
Brigatinib	Ph I ALK-naïve and crizotinib resistant (93)	46	15	53	NA	icPFS: 15.6	18.9
	ALTA. Ph II in crizotinib-resistant (94, 95)	153	18	67[e]	NA	icPFS: 18.4[e]	NR[e]

icRR, intracranial response rate; icTTP, intracranial time to progression; s/icPFS, systemic/intracranial progression-free survival (PFS); icDOR, intracranial duration of response; CT, chemotherapy; NA, not available; NR, not reached.

[a]*ALK TKI naïve and chemotherapy-naïve or up to three lines of chemotherapy with progression during or after the last chemotherapy regimen.*

[b]*Data reported for previously untreated BM/previously treated BM.*

[c]*12-week intracranial disease control rate.*

[d]*Results expressed as ALK inhibitor-naïve patients, ALK inhibitor-pretreated patients.*

[e]*Patients receiving 180 mg/day.*

Remon J, Besse B. *Front Oncol* 2018;8:88.

Management of Brain Metastases from Non-Small Cell Lung Cancer

- SRS is preferred for the preservation of neurocognitive function in patients with oligometastases.
- Whole brain radiotherapy is reserved for those with multiple brain metastases or poor performance status.
- Targeted therapy are becoming the first-line treatment in oncogene-addicted NSCLC patients with no or minimal symptoms

Beth Israel Deaconess Medical Center

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